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# Shortened Maximum Likelihood Estimation of Rh Gene Frequencies[1, 2]

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THE Rh BLOOD TYPES provide a good example of the classification of a population into several phenotypes determined by a known number of genes. If tests are made with the usual four sera, anti-C, anti-D, anti-E and anti-c, we can classify all individuals into the following twelve phenotypes, where a large letter represents a positive reaction and a small letter a negative reaction, except that small c represents a positive reaction with anti-c, and C is repeated to indicate a negative reaction with anti-c.

| | |
|---|---|
| 1. cde | 7. CDe/c |
| 2. cdE | 8. CDE/c |
| 3. cDe | 9. Cde/C |
| 4. cDE | 10. CdE/C |
| 5. Cde/c | 11. CDe/C |
| 6. CdE/c | 12. CDE/C |

These phenotypes can be accounted for by the assumption that they result from the various combinations of 8 genes. If phenotype 10 is missing, as it usually is, the rare (though probably present) gene $R_y$ may be omitted from consideration, and the data fitted by adjustment of the frequencies of 7 genes, $r$, $R_0$, $R''$, $R_2$, $R'$, $R_1$, and $R_z$.

For estimation of the frequencies of these genes, square root methods analogous to those often used for ABO data have been published by Race, Mourant and McFarlane (15), but these methods suffer from the inefficiency of square root methods in general (4, 17).

A method of calculating maximum likelihood estimates of these gene frequencies has been presented by Fisher (8, 9). This method involves the construction of 7 by 7 matrices, and the inversion of 6 by 6 matrices, and also, since it makes use of a change of variables, requires further rather complicated operations upon the results obtained before the gene frequencies as such

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[2] This paper was part of the symposium "Genetics and the Races of Man", sponsored by the American Society of Human Genetics, The Society for the Study of Evolution, and The American Society of Naturalists, presented at the meeting of the AAAS in Boston, December, 1953.

emerge. It has generally been considered difficult; Race and Sanger (16) say that "it is hardly for the non-mathematician."

It was pointed out by Fisher in his second paper on the subject that the sum of the genes containing C (*viz.* $R_1$, $R'$, $R_z$ (and $R_y$ if present )) must, when they are accurately calculated, equal the value obtained by simple gene counting, which is C = CDE/C + CDe/C + CdE/C + Cde/C + (½)CDE/c + (½)CDe/c + (½)CdE/c + (½)Cde/c, where CDE/C, etc. represent the relative frequencies of the various phenotypes. Similarly the sum of the c-containing genes, $r$, $R''$, $R_0$, and $R_2$ must equal cde + cdE + cDe + (½)CDE/c + (½)CDe/c + (½)CdE/c + (½)Cde/c. Also, of course, c = 1 − C.

This suggests that it might be possible to take the values of C and c as fixed from the beginning, and estimate by maximum likelihood merely the relative proportions of the genes $R_1$, $R'$ and $R_z$ among the C-containing genes, and of $r$, $R''$, $R_0$ and $R_2$ among the c-containing genes. All that is needed is the proportion of the C-containing genes which contain D, and of these the proportion which contain E, etc. We can in fact see that if we omit, as does Fisher, the rare gene $R_y$, which however could be included if desired by a simple extension of the method, we can write the frequencies of the 7 common Rh genes as follows

| *Gene* | *Frequency* |
|---|---|
| $r$ = cde | c $uv$ |
| $R''$ = cdE | c $u(1-v)$ |
| $R_0$ = cDe | c $(1-u)w$ |
| $R_2$ = Cde | c $(1-u)(1-w)$ |
| $R'$ = CDe | C $x$ |
| $R_1$ = CDe | C $(1-x)z$ |
| $R_z$ = CDE | C $(1-x)(1-z)$ |

In these formulas the symbols on the left represent the 7 common genes, or "chromosomes", and on the right c represents the total frequency of c-containing genes, determined by gene counting as outlined above, and C the total frequency of the C-containing genes, or 1 − c. The symbols $u$, $v$, $w$, $x$ and $z$ represent the following ratios: $u = (r + R'')/c$, $v = r/(r + R'')$, $w = R_0/(R_0 + R_2)$, $x = (R' + R_y)/\mathrm{C}$ (if $R_y$ is present) $= R'/\mathrm{C}$ (if $R_y$ is not present), $z = R_1/(R_1 + R_z)$.

It will be seen that, for the usual problem where gene $R_y$ is not encountered, this reduces the problem to the determination of 5 unknowns, $u$, $v$, $w$, $x$, and $z$, and only involves the construction and inversion of 5 by 5 matrices instead of 7 by 7 and 6 by 6 matrices. Since the work of inverting a matrix is proportional to the cube of the order (2), this reduces the labor to 125/216 = 58 per cent of that involved in dealing with the bigger matrices. If the labor of constructing a matrix is also proportional to the cube of its order, as it may well be, then this method reduces the labor of constructing the matrix, which is also very con-

TABLE 1.—EXPECTED FREQUENCIES OF THE TWELVE PHENOTYPES DISTINGUISHABLE BY USE OF FOUR ANTI-Rh SERA

| Phenotype | Frequency |
|---|---|
| 1. cde | $c^2 u^2 v^2$ |
| 2. cdE | $c^2 u^2 (1 - v^2)$ |
| 3. cDe | $c^2[(1 - u)^2 w^2 + 2u(1 - u)vw]$ |
| 4. cDE | $c^2[(1 - u)^2(1 - w^2) + 2u(1 - u)(1 - vw)]$ |
| 5. Cde/c | $2Cc\ uxv$ |
| 6. CdE/c | $2Cc\ ux(1 - v)$ |
| 7. CDe/c | $2Cc\ [(1 - u)(1 - x)wz + u(1 - x)vz + (1 - u)xw]$ |
| 8. CDE/c | $2Cc[(1 - u)(1 - w) + u(1 - x)(1 - v) + (1 - u)(1 - x)w(1 - z) + u(1 - x)v(1 - z)]$ |
| 9. Cde/C | $C^2 x^2$ |
| 10. Usually missing | |
| 11. CDe/C | $C^2 [(1 - x)^2 z^2 + 2x(1 - x)z]$ |
| 12. CDE/C | $C^2 [(1 - x)^2(1 - z^2) + 2x(1 - x)(1 - z)]$ |

siderable, to $125/343 = 36.5$ per cent of that of the construction in the older method. In addition, the process of getting from the parameters $u$, $v$, $w$, $x$ and $z$ to the gene frequencies is somewhat simpler than getting from Fisher's $x_1$, $x_2$, etc. to the gene frequencies.

From the gene combinations represented by each of the 12 phenotypes distinguishable by use of the four anti-Rh sera, anti-C, anti-D, anti-E and anti-c, it is easy to rewrite the expected values in terms of our new parameters $u$, $v$, $w$, $x$, and $z$ (table 1).

By ordinary partial differentiation we get the formulas for the derivatives of the expected values for the five parameters. These are needed for calculating the "discrepancies" $\partial L/\partial u$, $\partial L/\partial v$, etc., and for constructing the "information matrix" (see table 2). Note that the sum of these derivatives is zero for each column, and for each column the sub-totals must be zero for items 1–4, 5–8 and 9–12. These observations provide important checks on the calculations.

Needless multiplication may be avoided by not multiplying in the $C^2$, 2Cc and $c^2$ (and $N$, the total number tested) until they are needed. In the table of $(1/F)(\partial F/\partial p)$ (see table 4) which is to be constructed from table 2 these values would cancel put anyway, except that a factor of 2 would remain in rows 1–4 and 9–12. This factor can be put in when needed.

The reason for these preliminaries may now be seen. To proceed by the method of maximum likelihood, we should now write

$$L = A_1 \log f_1 + A_2 \log f_2 + \cdots$$

where $L$ represents the logarithm of the likelihood function, $A_1$, $A_2$, etc. are the observed numbers in the various classes, and $f_1$, $f_2$, etc. are the expected frequencies of the various classes, expressed in terms of the parameters it is de-

TABLE 2.—PARTIAL DERIVATIVES OF THE EXPECTED FREQUENCIES

| Phenotype | $\partial F/\partial u$ | $\partial F/\partial v$ | $\partial F/\partial w$ | $\partial F/\partial x$ | $\partial F/\partial z$ |
|---|---|---|---|---|---|
| 1 | $2c^2uv^2$ | $2c^2u^2v$ | 0 | 0 | 0 |
| 2 | $2c^2u(1-v^2)$ | $-2c^2u^2v$ | 0 | 0 | 0 |
| 3 | $2c^2[(1-2u)vw - (1-u)w^2]$ | $2c^2u(1-u)w$ | $2c^2[(1-u)^2w + u(1-u)v]$ | 0 | 0 |
| 4 | $2c^2[(1-2u)(1-vw) - (1-u)(1-w^2)]$ | $-2c^2u(1-u)w$ | $-2c^2[(1-u)^2w + u(1-u)v]$ | 0 | 0 |
| 5 | $2Ccxv$ | $2Ccux$ | 0 | $2Ccuv$ | 0 |
| 6 | $2Ccx(1-v)$ | $-2Ccux$ | 0 | $2Ccu(1-v)$ | 0 |
| 7 | $-2Cc[(1-x)wz - (1-x)vz + xw]$ | $2Ccu(1-x)z$ | $2Cc[(1-u)(1-x)z + (1-u)x]$ | $-2Cc[(1-u)wz + uvz - (1-u)w]$ | $2Cc[(1-u)(1-x)w + u(1-x)v]$ |
| 8 | $2Cc[(w-1) + (1-x)(1-v) - (1-x)w(1-z) + (1-x)v(1-z)]$ | $-2Ccu(1-x)z$ | $2Cc[(u-1) + (1-u)(1-x)(1-z)]$ | $-2Cc[u(1-v) + (1-u)w(1-z) + uv(1-z)]$ | $-2Cc[(1-u)(1-x)w + u(1-x)v]$ |
| 9 | 0 | 0 | 0 | $2C^2x$ | 0 |
| 11 | 0 | 0 | 0 | $-2C^2[(1-x)z^2 - (1-2x)z]$ | $2C^2[(1-x)^2z + x(1-x)]$ |
| 12 | 0 | 0 | 0 | $-2C^2[(1-x)(1-z^2) - (1-2x)(1-z)]$ | $-2C^2[(1-x)^2z + x(1-x)]$ |

sired to estimate. We now find the values of the parameters for which the partial derivatives $\partial L/\partial u$, $\partial L/\partial v$, etc. of the logarithm of the likelihood function equal zero. In practice it turns out that the equations resulting from setting these expressions equal to zero can not be solved directly, but we may make use of methods similar to Newton's method of approximation for getting the root of an equation to calculate suitable corrections for the trial values of the parameters (8, 17).

Instead of working out the explicit expressions for $\partial L/\partial u$, $\partial L/\partial v$, etc., it proves simpler to calculate them from the relations

$$\partial L/\partial u = \sum A(1/F)(\partial F/\partial u)$$

$$\partial L/\partial v = \sum A(1/F)(\partial F/\partial v), \text{ etc.}$$

where $A$ signifies the observed number in a class, $F$ is the expected number, and $\Sigma$ means summation for all classes.

The method of maximum likelihood requires that values of the parameters be found which make $\partial L/\partial u$, $\partial L/\partial v$, etc., each equal to zero. Using trial values for the parameters, we shall find these expressions small, but not equal to zero. We wish to calculate the corrections to $u$, $v$, etc.

If we had only one parameter $p$, the correction to a trial value $p'$ could be found by dividing $(\mathrm{d}L/\mathrm{d}p)_{p=p'}$ by $-(\mathrm{d}^2L/\mathrm{d}p^2)_{p=p'}$, which is just Newton's method. When we have several parameters, as in the present case, we have to divide the column-vector of the discrepancies $\partial L/\partial u$, $\partial L/\partial v$, etc., by the matrix of the negative second derivatives $-\ \partial^2L/\partial u^2$, $-\ \partial^2L/\partial v^2 \ldots -\partial^2L/\partial u\partial v$, $-\ \partial^2L/\partial u\partial w \ldots$, which means multiplying by the reciprocal of the matrix of the negative second derivatives. This means we have to construct the matrix of the second derivatives and invert it.

It proves convenient not to derive explicit expressions for the second derivatives but to make use of the fact that

$$-\sum F(d^2/\mathrm{d}p^2)(\log F) = \sum(1/F)(\mathrm{d}F/\mathrm{d}p)^2$$

which enables us to calculate the second derivatives from the first partial derivatives of the expected values.

Now it can be shown that under rather general conditions the variance (6, 11) of the maximum likelihood estimate of a parameter is

$$V_{pp} = -1/(\mathrm{d}^2L/\mathrm{d}p^2)$$

and since Fisher (10) defined the quantity of information about a parameter as $1/V_{pp}$, it is customary to call the negative second derivatives the "informa-

TABLE 3.—PARTIAL DERIVATIVES

| Phenotype | $\partial F/\partial u$ | $\partial F/\partial w$ | $\partial F/\partial x$ | $\partial F/\partial z$ |
|---|---|---|---|---|
| 1 | .586893 | 0 | 0 | 0 |
| 3 | −.164981 | .320218 | 0 | 0 |
| 4 | −.421912 | −.320218 | 0 | 0 |
| 5 | .034978 | 0 | .586893 | 0 |
| 7 | .491371 | .399482 | −.560401 | .748033 |
| 8 | −.526349 | −.399482 | −.026492 | −.748033 |
| 9 | 0 | 0 | .034978 | 0 |
| 11 | 0 | 0 | −.001928 | .933194 |
| 12 | 0 | 0 | −.033050 | −.933194 |

tion matrix" and to represent the elements of this matrix by the symbols $I_{uu}$, $I_{uv}$, etc. The reciprocal[3] of $\{I\}$ is $\{V\}$, the covariance matrix.

We proceed in the present case as follows: calculate the expected frequencies, and the partial derivatives (table 3). Construct table 4 by dividing the values of the partial derivatives in each row of table 3 by the expected frequencies.[4] From this table calculate the "discrepancies" by multiplying the elements in each column by: for rows 1–4, twice the observed numbers; for rows 5–8, the observed numbers; for rows 9–12, twice the observed numbers (the factor 2 is needed for rows 1–4 and 9–12 because it has been left out in constructing the table of partial derivatives). The sums for the various columns give $\partial L/\partial u$, $\partial L/\partial v$, etc. The multiplications are done by using the cumulative multiplication device of the calculating machine.

Now construct the information matrix by multiplying corresponding values of $\partial F/\partial p$ (table 3) and $(1/F)$ $(\partial F/\partial p)$ (table 5), and adding. Thus the first element $I_{uu}$ of the information matrix is the sum for all phenotype classes of the terms $(\partial F/\partial u)(1/F)(\partial F/\partial u)$, the second element $I_{uv}$ is the sum of $(\partial F/\partial u)$ $(1/F)(\partial F/\partial v)$, etc.

Before making these multiplications the values of $c^2$, Cc, $C^2$, $N$(the total number tested) and the required factors of 2 are inserted by multiplying the first four rows of either the $(\partial F/\partial p)$ table (table 3), or the $(1/F)(\partial F/p)$ table (table 4) by $4c^2N$, rows 5–8 by $2CcN$, and rows 9–12 by $4C^2N$. Suppose we select table 4 for this treatment. This gives table 5.

The information matrix is now inverted in the usual way (a numerical example is given below). The corrections for the parameters $u$, $v$, $w$, etc. are then

[3] For those unfamiliar with matrix algebra, it may be mentioned that nothing more complicated than the solution of five simultaneous equations in five unknowns is involved in getting the reciprocal, or inverse, of the matrix involved here (1, 3).

[4] Inspection of tables 1 and 2 reveals that some of the items of table 4 can be calculated more simply than by the process just described, with some gain in accuracy. Thus we see that $(1/F)(\partial F/\partial u)$ for phenotype class 1 is equal to $uv^2/u^2v^2 = 1/u$. Similarly $(1/F)(\partial F/\partial u)$ for class 5 $= 1/u$, and $(1/F)(\partial F/\partial x) = 1/x$ for classes 5 and 9. This serves as a useful check, or if desired, these items can be calculated directly by taking the reciprocals of $u$ and $x$, as was done in the present calculations.

TABLE 4

| Phenotype | $(1/F)(\partial F/\partial u)$ | $(1/F)(\partial F/\partial w)$ | $(1/F)(\partial F/\partial x)$ | $(1/F)(\partial F/\partial z)$ | |
|---|---|---|---|---|---|
| 1 | 1.703889 | 0 | 0 | 0 | 24 |
| 3 | −.643434 | 1.248866 | 0 | 0 | 18 |
| 4 | −1.057029 | −.802252 | 0 | 0 | 24 |
| 5 | 1.703888 | 0 | 28.589390 | 0 | 2 |
| 7 | .673986 | .547947 | −.768671 | 1.026035 | 64 |
| 8 | −2.101856 | −1.595241 | −.105790 | −2.987101 | 24 |
| 9 | 0 | 0 | 28.589390 | 0 | 0 |
| 11 | 0 | 0 | −.002064 | .999243 | 150 |
| 12 | 0 | 0 | −.509441 | −14.384493 | 10 |
| Discrepances | $\partial L/\partial u$ | $\partial L/\partial w$ | $\partial L/\partial x$ | $\partial L/\partial z$ | |
| | .041164 | .008364 | .040866 | .017336 | |

TABLE 5

| | | | | |
|---|---|---|---|---|
| 1 | 204.265 | 0 | 0 | 0 |
| 3 | −77.136 | 149.716 | 0 | 0 |
| 4 | −126.719 | −96.175 | 0 | 0 |
| 5 | 163.674 | 0 | 2746.271 | 0 |
| 7 | 64.742 | 52.635 | −73.838 | 98.560 |
| 8 | −201.902 | −153.237 | −10.162 | −286.938 |
| 9 | 0 | 0 | 8802.151 | 0 |
| 11 | 0 | 0 | −.635 | 307.649 |
| 12 | 0 | 0 | −156.848 | −4428.723 |

obtained by multipying the elements of each column of the inverted (or covariance) matrix by the discrepancies $\partial L/\partial u$, $\partial L/\partial v$, etc. (the top element by $\partial L/\partial u$, the second down by $\partial L/\partial v$, etc.) and summing for each column. The sum for the first column gives the correction for $u$, that for the second column for $v$, etc.

After the corrected values of $u$, $v$, $w$, $x$ and $z$ have been obtained, we may calculate the gene frequencies by the formulas on page 304.

The variance of c, which is the same as the variance of C, is given by the formula (17):

$$V(\mathrm{c}) = V(\mathrm{C}) = \mathrm{c}(1 - \mathrm{c})/2N = \mathrm{Cc}/2N$$

Our gene frequencies result from multiplying the estimates of c and C, already obtained, by the various ratios $u$, $v$, $w$, $x$ and $z$. I am indebted to Prof. Norton (14) for pointing out to me the correct formula for the variance of a product of two variables $x$ and $y$. This formula is

$$V(xy) = [E(x)]^2V(y) + 2[E(x)][E(y)]CV(x, y) + [E(y)]^2 V(x)$$

where $V$ is the variance and $CV$ the covariance, and $E(x)$ and $E(y)$ the values of $x$ and $y$ as estimated, the variances of the estimates of $u$, $v$, $w$, $x$, and $z$ are the diagonal elements of the covariance matrix, and the covariances are the appropriate off-diagonal terms. Since C and c are independent of $u$, $v$, $w$, $x$, and $z$, in computing the variance of a value multiplied by C or c no covariance term is used.[5]

Repeated application of this formula allows the variances of the estimated gene frequencies to be calculated. From the variances the standard deviations are obtained by extracting the square root.

As a numerical illustration we may take the calculations for my data on the Punjabis of Lahore (5). The raw data are

| *Phenotype* | *Number Observed* |
|---|---|
| CDe/C | 75 |
| CDe/c | 64 |
| cDE | 12 |
| CDE/c | 24 |
| cde | 12 |
| CDE/C | 5 |
| cDe | 9 |
| Cde/c | 2 |
| Total | 203 |

We obtain the total of the C-containing genes by simple counting and dividing by the number examined. We find

$$C = [CDe/C + (CDe/c)/2 + (CDE/c)/2 + CDE/C + (CDe/c)/2]/203$$
$$= 0.615763547.$$

Similarly,

$$c = [(CDe/c)/2 + cDE + (CDE/c)/2 + cde + cDe + (Cde/c)/2]/203$$
$$= 0.384236453.$$

Preliminary estimates of the gene frequencies $r$, $R_0$ etc. can be obtained by Mourant's method (12) and the ratios $u$, $v$, etc. calculated from them by the formulas on page 3. Or the ratios $u$, $v$, etc. could be estimated roughly directly from the data. Mourant's method gives better results, and the calculations for the present data began with frequencies so estimated. To illustrate the convergent nature of the process, the calculation given here is the third successive round of calculations based on these frequencies.

Since the phenotype cdE is missing in the present data, $R''$ is taken to be

[5] The variances are the diagonal elements of the inverted matrix, and the covariances are the off-diagonal elements. Thus, in the example given below, the variance of $u$ is 4.312608 ($\times 10^{-3}$) and the covariances $CV(u, w)$, $CV(u, x)$ and $CV(u, z)$ are $-3.237717$, $-.181061$, and $-.073022$ (all times $10^{-3}$). The variance of $1 - u$ is the same as the variance of $u$. Note, however, that $CV((1 - u)w)$ is the negative of $CV(u, w)$.

zero, and the ratio $v = 1$. This means that $v$ is replaced by 1 in all calculations and no partial derivatives are calculated for it. This reduces the number of independent parameters to be estimated in the present case to four, with corresponding simplifications in the calculations.

First we construct a table of the estimated ratios and certain functions of them which are repeatedly needed in the calculations. Let $a$ be the general symbol for one of the ratios $u$, $w$, $x$ and $z$. Then we find

| Ratio | $a$ | $1-a$ | $a^2$ | $1-a^2$ | $(1-a)^2$ |
|---|---|---|---|---|---|
| $u$ | .586893 | .413107 | .344443 | | .170657 |
| $w$ | .455699 | .544301 | .207662 | .792338 | |
| $x$ | .034978 | .965022 | .001223(46) | | .931267 |
| $z$ | .965823 | .034177 | .932814 | .067186 | |

Omitting for the time being the factors $c^2$, $C^2$ and 2Cc, we obtain for the expected frequencies

| | |
|---|---|
| 1. cde | .344443 |
| 3. cDe | .256407 |
| 4. cDE | .399149 |
| 5. Cde/c | .020528 |
| 7. CDe/c | .729052 |
| 8. CDE/c | .250421 |
| 9. Cde/C | .001223(46) |
| 11. CDe/C | .933901 |
| 12. CDE/C | .064875 |

For purposes of numerical check, note that items 1–4 must add up to one, as must items 5–8 and items 9–12.

In maximum likelihood calculations of this sort, it is desirable to retain at least two places of decimals more than are desired in the final results (9). In the present example the number of decimal places used in the calculations would justify confidence in four decimal places in the gene frequencies. Since these calculations are offered merely as an illustration of the method, five decimal places have been given in the final results, although this would not in general be defensible.

Now calculate the partial derivatives of the expected frequencies, omitting the factors $2c^2$, etc.

Then divide the partial derivatives by the expected frequencies ($F$). This gives table 4. Use this table for calculating the "discrepancies" $\partial L/\partial u$, $\partial L/\partial w$, etc., which will be needed later for the calculation of the corrections.

The numbers on the right are the observed numbers in the respective classes, multiplied by 2 in the case of rows 1–4 and 9–12 (this factor 2 develops from neglecting it in the table of partial derivatives). The discrepancies are calculated by multipying each element of a column by the numbers on the right, and summing for each column.

Now multiply rows 1–4 of table 4 by $4c^2N$, rows 5–8 by $2CcN$, and rows 9–12 by $4C^2N$ (where $N$ is the total number tested). We thus obtain table 5.

Now form the information matrix. Multiplying each element of column 1 of table 3 by the corresponding element of column 1 of table 5 and summing gives the first element of the first row ($I_{uu}$) of the information matrix. Then obtain the second element ($I_{uv}$) by multiplying each element of column 1 of table 3 by the corresponding element of column 2 of table 5 and summing, and so on. Then to obtain the covariance matrix the information matrix is inverted. We now proceed to do this.

It is most convenient, when the information matrix is larger than 3 by 3, to arrange the calculations by the Doolittle method (18).

| *Information matrix* | | | | *Constant terms* | | | | *Check column* |
|---|---|---|---|---|---|---|---|---|
| 329.880 | 122.397 | 65.126 | 199.459 | 1 | 0 | 0 | 0 | 717.862 |
| 122.397 | 160.981 | −25.437 | 154.000 | 0 | 1 | 0 | 0 | 412.941 |
| 65.126 | −25.437 | 1966.482 | 98.145 | 0 | 0 | 1 | 0 | 2105.316 |
| 199.459 | 154.000 | 98.145 | 4708.319 | 0 | 0 | 0 | 1 | 5160.923 |

The information matrix appears on the left, and its elements constitute the coefficients of the four simultaneous equations which it is necessary to solve. The numbers on the right are the constant terms of these equations. The check column is formed each time by adding all the numbers in a row.

Now divide each row by the right hand member of the information matrix (row 1 is divided by 199.459, for example). Divide the numbers in the check column too. We obtain

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1.653874 | .613645 | .326513 | 1 | 5.013561 | 0 | 0 | 0 | 3.599046 |
| .794786 | 1.045331 | −.165175 | 1 | 0 | 6.493506 | 0 | 0 | 2.681436 |
| .663569 | −.259178 | 20.036497 | 1 | 0 | 0 | 10.189006 | 0 | 21.451077 |
| .042363 | .032708 | .020845 | 1 | 0 | 0 | 0 | .212390 | 1.096128 |

All the numbers in columns 5, 6, 7 and 8 have been multiplied by $10^3$ to avoid writing in a lot of zeros.

Now subtract the last row from each of the others in turn.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1.611511 | .580937 | .305668 | 5.013561 | 0 | 0 | −.212390 | 2.502918 |
| .752423 | 1.012623 | −.186020 | 0 | 6.493506 | 0 | −.212390 | 1.585308 |
| .621206 | −.291886 | 20.015652 | 0 | 0 | 10.189006 | −.212390 | 20.354949 |

Now divide by each number in the third column. Continue to proceed in this way until only a single number remains in column 1.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5.272096 | 1.900549 | 1 | 16.401982 | 0 | 0 | −.694839 | 8.188352 |
| −4.044850 | −5.443624 | 1 | 0 | −34.907569 | 0 | +1.141759 | −8.522242 |
| .031036 | −.014583 | 1 | 0 | 0 | .509052 | −.010611 | 1.016952 |
| | | | | | | | |
| 5.241060 | 1.915132 | | 16.401982 | 0 | −.509052 | −.684228 | 7.171400 |
| −4.075886 | −5.429041 | | 0 | −34.907569 | −.509052 | 1.152370 | −9.539194 |
| | | | | | | | |
| 2.736657 | 1 | | 8.564413 | 0 | −.265805 | −.357275 | 3.744597 |
| .750756 | 1 | | 0 | 6.429785 | .093765 | −.212260 | 1.757068 |
| | | | | | | | |
| 1.985901 | | | 8.564413 | −6.429785 | −.359570 | −.145015 | 1.987529 |

The first row of the inverted matrix is now obtained by dividing the 2nd, 3rd, 4th and 5th numbers in the last row by the first (i.e., by 1.985901). Then the next row is found by multiplying each of these numbers by 2.736657, changing sign, and adding successively to the numbers in the same row with 2.736657 (except the check column, which is disregarded from now on). Continuation of similar operations gives the remaining elements of the inverted matrix, which is the covariance matrix.

*Covariance matrix (times $10^3$)*

| | | | |
|---|---|---|---|
| 4.312608 | −3.237717 | −.181061 | −.073022 |
| −3.237716 | 8.860521 | .229697 | −.157439 |
| −.181063 | .229701 | .518021 | −.010639 |
| −.073022 | −.157438 | −.010641 | .220855 |

The corrections $\delta u$, $\delta w$, $\delta x$, and $\delta z$ to be applied to the estimates of the parameters are now found by multiplying successively each element of a column of the covariance matrix by the discrepancies $\partial L/\partial u$, $\partial L/\partial w$, etc., and adding. Thus the correction to be applied to $u$ is given by the sum of

$$(4.312608)(10^{-3})(.041164)$$
$$(-3.237716)(10^{-3})(.008364)$$
$$(-.181063)(10^{-3})(.040866)$$
$$(-.073022)(10^{-3})(.017336)$$

and equals 0.141779 times $10^{-3}$. Similarly $\delta w = -0.052510$ times $10^{-3}$, $\delta x =$ 0.015453 times $10^{-3}$, and $\delta z = -0.000929$ times $10^{-3}$. Applying these corrections, we get for the corrected values of the parameters

$$u = 0.587035, \quad w = 0.455646, \quad x = 0.034993, \quad z = 0.965822$$

From these the corrected values of the gene frequencies are calculated

$$\begin{aligned} r &= cu &&= 0.225560 \\ R_0 &= c(1-u)w &&= 0.072300 \\ R_2 &= c(1-u)(1-w) &&= 0.086376 \\ R &= Cx &&= 0.021547 \\ R_1 &= C(1-x)z &&= 0.573907 \\ R_z &= C(1-x)(1-z) &&= 0.020309 \end{aligned}$$

The standard deviations of the parameters $u$, $w$, $x$, and $z$ can be obtained by taking the square roots of the diagonal elements of the covariance matrix. Variances, and from these the standard deviations, of the estimated gene frequencies can be obtained by the formulas given on page 309.

The approximation process converges fairly rapidly, as shown in table 6, which shows the successive corrections obtained, starting with parameters calculated from frequencies estimated by Mourant's method. For comparison the standard deviations of the estimated parameters are shown. It will be seen that even the first set of corrections are small compared with the standard

TABLE 6.—CORRECTIONS TO THE PARAMETERS $u$, $w$, $x$ AND $z$ OBTAINED BY SUCCESSIVE APPLICATION OF THE APPROXIMATION METHOD OF THE PRESENT PAPER TO ESTIMATES OBTAINED BY MOURANT'S METHOD (13), COMPARED WITH THE STANDARD DEVIATIONS OF THE MAXIMUM LIKELIHOOD ESTIMATES OF THE PARAMETERS

| Parameter | First Correction | Second Correction | Third Correction | Standard Deviation of Estimates |
|---|---|---|---|---|
| $u$ | +0.002846 | −0.000183 | +0.000142 | 0.065670 |
| $w$ | +0.001461 | +0.000258 | −0.000053 | 0.094130 |
| $x$ | +0.002509 | +0.000149 | +0.000015 | 0.022760 |
| $z$ | −0.001409 | −0.000008 | −0.000001 | 0.014861 |

TABLE 7.—CORRECTIONS TO PARAMETERS OBTAINED BY SUCCESSIVE APPLICATIONS OF THE PRESENT METHOD TO ESTIMATES OBTAINED BY CRUDE SQUARE ROOT METHODS

| Parameter | First Correction | Second Correction | Standard Deviation |
|---|---|---|---|
| $u$ | −0.048507 | +0.000314 | 0.065646 |
| $w$ | +0.006522 | −0.000603 | 0.094059 |
| $x$ | +0.002586 | +0.000005 | 0.022761 |
| $z$ | −0.000401 | +0.000002 | 0.014726 |

deviations of the maximum likelihood estimates. (It is doubtful if this would always be the case). The adjustment process has been repeated here to illustrate that the process is approaching the exact maximum likelihood values, for which the calculated discrepancies $\partial L/\partial u$ etc. would be zero, as Fisher (9) demonstrated for his method. The above calculations were those involved in the third application of the method.

Considering the relative simplicity of Mourant's method, there would seem to be no valid reason for not starting with estimates obtained by it, and adjusting by the present method if desired. In some cases the first adjustments would presumably be of the same order of magnitude as the standard deviations, and thus quite necessary, although this has not happened in any case I have actually computed. (In the case of the above data the corrections are borderline; see below). In addition, the present method has the merit of giving estimates of the standard deviations of the adjusted estimates.

Even if the cruder estimates derived by the older square root methods are used for a starting point the process converges rapidly, at least in the case of the above set of data. This is shown in table 7. It is clear that the corrections are negligible after the first set. Fisher states (10) "In approaching the maximum likelihood solution by successive approximations we have seen that starting with an inefficient statistic, a single process of approximation will in ordinary cases give an efficient statistic differing from the maximum likelihood solution, by a quantity which with increasing samples decreases as $n^{-1}$." In cases where the first or second adjustments are not small compared with

the standard error, the decision to terminate the calculations should be based on the size of the last adjustments and the stability of the covariance matrix.

It often happens that after the covariance matrix has been recalculated once it does not change much in future repetitions of the process. In such cases it can be used, together with the new discrepancies, to calculate further successive corrections, thus avoiding the labor of inverting a new matrix each time.

No general rule governing the degree of approximation to the true maximum likelihood values which is desirable in such calculations seems to have been published. Stevens (17) says one process of adjustment is adequate, but this is not always so. The question is connected with the problem of how many decimal places ought to be given in the final results. Some blood group workers have apparently been considerably distressed at the number of decimal places reported by other investigators, pointing out that in a series of 200 subjects, an error in determining the blood group of one individual would alter the raw percentage frequencies by 0.5, which could amount to considerably more than 1 per cent of the frequency itself. Such workers have implied doubts as to the usefulness of making the maximum likelihood adjustments at all.

Statistical calculation can of course do nothing about errors in the data. Few of us never make mistakes, and each worker must judge for himself the intrinsic reliability of the data themselves. But aside from this subjective evaluation, we can only ask of a set of data, what information does it contain, taken at face value?

It would seem that the sensible way to decide the question of how good an approximation to the true maximum likelihood estimates is adequate is by weighing the computational labor against the serological work, already put in, which would be sacrificed if the computations were not done. Let us assume, for instance, that the worker has returned from the field with as many determinations as opportunity allowed him to carry out. Let us also assume that he has not knowingly included any erroneous determinations. His body of data contains just so much information about the population studied, and it is desired to make estimates of the gene frequencies which do not waste much of this information, unless the cost of making the estimates is greater than the cost of going back and making more determinations. This will certainly seldom be the case. Prof. Norton (14) has suggested that a good general rule is to waste no more than one per cent of the data. This means that the variance of the estimate should not exceed 101 per cent of the variance of the true maximum likelihood estimate. If this is so, the variance of the difference between the two estimates is less than 1 per cent of the likelihood variance, and the standard deviation is less than 10 per cent of the likelihood standard deviation. Therefore, if the last adjustment is as little as one-tenth of a standard error, it is reasonably certain that less than one percent of the information is being wasted.

TABLE 8.—GENE FREQUENCIES FOR THE PUNJABIS CALCULATED BY VARIOUS METHODS

| Gene | Square root (13) | Mourant (12) | Boyd (this paper) | Standard deviations of maximum likelihood estimates |
|---|---|---|---|---|
| $R_2$ | 0.0506 | 0.0872 | 0.08638 | 0.015043 |
| $R_0$ | 0.0787 | 0.0725 | 0.07230 | 0.023575 |
| r | 0.2429 | 0.2245 | 0.22556 | 0.028940 |
| $R_z$ | 0.0199 | 0.0195 | 0.02031 | 0.008865 |
| R′ | 0.0198 | 0.0199 | 0.02155 | 0.014040 |
| $R_1$ | 0.5881 | 0.5763 | 0.57390 | 0.027838 |
| $\chi^2$ | 10.340 | 1.202 | 1.152 | |

It has been proposed to decide on the number of decimal places to be retained by use of the "one-third sigma rule" (12), which states that a published statistic should be terminated with the decimal place given by the first figure of one-third of its standard error. It can be shown (14) that the loss of information which results from rounding off in the usual way to this number of decimal places is less than 1 per cent. In the present case the first figure of one-third of the standard deviations of the gene frequencies falls in each case in the third place to the right of the decimal point, and we should therefore report three decimal places. More have been given in table 8, however, since the purpose of the paper was partly pedagogic.

## COMPARISON WITH OTHER METHODS

For purposes of comparison, I have calculated the gene frequencies from the data on the Punjabis by the square root method of Race, Mourant and McFarlane (15) (cf. 16). The results are given in table 8.

Values of $\chi^2$ have been calculated for the three sets of frequencies, first amalgamating all expected classes of 5 or less. It will be seen from a table of $\chi^2$, entered with two degrees of freedom, that the square root estimates significantly fail to fit the data, whereas the results of Mourant's method and of the maximum likelihood method show no significant discrepancy.

Mourant's methods, although not maximum likelihood methods, are seen to give in this case results which are extraordinarily good. They will be described in full in his forthcoming book (13), but in the meantime I have permission to present them briefly here.

First compute rough values for the gene frequencies by square root methods as follows:

$$\begin{aligned} r &= \sqrt{\mathrm{cde}} \\ R' &= (\mathrm{Cde}/\mathrm{c})/2r \\ R'' &= \sqrt{\mathrm{cdE} + r^2} - r \\ R_z &= \sqrt{(R_1 + R')^2 + \mathrm{CDE}/\mathrm{C}} - (R_1 + R') \end{aligned}$$

$$R_0 = \sqrt{\text{cDe} + \text{cde}} - \sqrt{\text{cde}}$$
$$R_1 = \sqrt{R'^2 + \text{CDe/C}} - R'$$
$$R_2 = \sqrt{(R_0 + R'' + r)^2 + \text{cDE} - 2R_0R''} - (R_0 + R'' + r)$$

Now correct these preliminary estimates as follows: Multiply the values $R_1$, $R'$ and $R_z$ by the ratio $C/(R_1 + R' + R_z)$, where $C$ is the total frequency of C-containing genes as obtained by gene counting, or in other words:

$$C = (\text{2CDE/C} + \text{CDE/c} + \text{2CDe/C} + \text{CDe/c} + \text{2Cde/C} \\ + \text{Cde/c} + \text{2CdE/C} + \text{CdE/c})/2N.$$

Then multiply the estimates of $R_2$ and $R''$ by $(\text{E} - R_z)/(R_2 + R'')$, where $\text{E} = 1 - \sqrt{\text{cde} + \text{cDe} + \text{Cde/c} + \text{CDe/c} + \text{Cde/C} + \text{CDe/C}}$, and $R_z$ is the adjusted value just obtained.

Multiply the estimates of $R_0$ and $r$ by

$$(1 - (\text{C} + \text{E}) + R_z)/(R_0 + r)$$

where $R_z$ is again the adjusted value.

The frequencies so obtained add up to 1 exactly, and are in many cases (5) quite satisfactory, often differing from the maximum likelihood estimates by less than one standard error. The value of $\chi^2$ (table 8) shows the fit obtained in the present instance.

The maximum likelihood method described here has also been applied to the data used by Fisher (8, 9), and found to give the same adjusted gene frequencies as those found by him, to six places of decimals.

The present method, with appropriate modifications, can be used to estimate the gene frequencies from data resulting from tests with five Rh sera.

## SUMMARY

A simplified maximum likelihood method of obtaining the gene frequencies from Rh data is described. By taking advantage of the fact that the total frequency of genes containing C and genes containing c may be estimated directly from the data by gene counting, the order of the necessary matrices involved has been reduced from $7 \times 7$ and $6 \times 6$ to $5 \times 5$. A numerical example is worked out, and the results compared with those obtained by other methods.

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# Dermatoglyphics as Ethnic Criteria[1]

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THE UNIQUE VALUE of finger prints for identification is well known. As far back as two centuries BC the Chinese made thumb print impressions on clay documentary seals. Palm and foot prints are just as reliable as finger prints, but there is less likelihood of such impressions being left behind.

Dermatoglyphics possess great potentialities as a tool for human biologists, although comparatively few geneticists and anthropologists have made use of them. While they are inconspicuous traits and appear to be of no importance *per se*, they provide valuable, and in some respects unique types of information. Unlike skeletal dimensions, pigmentation, body conformation, features, disease resistance, longevity, and a host of quantitative variations, they are fully established during the first half of fetal development, and are not affected (except in total size), by postnatal circumstances. Age, nutrition, climatic variations and other post-natal factors render accurate heritability estimates of most standard anthropometric variations difficult, to say the least. The advantages of dermatoglyphics in this respect can hardly be over-emphasized.

It follows that significant correlations between the occurrence of particular kinds of dermatoglyphic configurations with other traits cannot be attributed to post-natal environmental circumstances. Mongoloid idiocy provides an example of such an association. Hand prints provide perhaps the best physical criterion of the abnormality. The hand prints of affected individuals are characterized by highly transverse main lines, relatively high frequencies of patterns in the second and third interdigital area, and low frequencies of patterns in the thenar/first and fourth interdigital areas. Main line D ends in position 13 in only about a quarter of one per cent of normal people, whereas approximately 5% of mongoloid idiots manifest it. Main line formula beginning with 11 occur in approximately ⅔ of the palms of mongoloids, but in only ⅓ of American Whites. In general, dextral trends are accentuated, (Snedeker, 1948).

Handedness also shows slight, but highly significant correlation with palmar dermatoglyphics. Left handers are characterized by lower bimanual asymmetry than are right-handers. This is best indicated in the thenar/first interdigital area where there is a highly significant increase in the occurrence of these

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patterns in the right palms of left-handers, as compared with those of right-handers.

Hand prints are easily and readily obtained. Such records may be kept indefinitely, and as only one sheet of paper is required per hand, they are not bulky. One is relieved of many of the worries accompanying investigations of blood groups, such as being certain the sera are kept in good condition, and that the tests are always correctly interpreted. Dermatoglyphics do not lie. Excellent prints may now be obtained through the use of sensitized paper and sensitizing fluid, thus rendering obsolete the former rather messy procedure of inking the fingers and palms.

## TWIN DIAGNOSIS

Dermatoglyphics are perhaps most extensively employed by biologists as criteria for twin diagnosis. Although they are not infallible, they are of outstanding importance for this purpose. The high heritability of dermatoglyphic configurations, plus bilateral asymmetries in their occurrence, provide the basis for their dependability in twin diagnosis.

Let us consider for a moment how bilateral asymmetries are of value. Patterns do not occur at random on the various finger tips and palmar areas. Whorls occur with greatest frequencies on ring fingers and thumbs, while arches occur most frequently on the middle and index fingers. Moreover, whorls occur more frequently on right than on left hands, whereas arches occur more frequently on lefts.

Palms manifest even greater bilateral asymmetries than do finger tips. Patterns occur almost twice as frequently in thenar/first interdigital and the fourth interdigital areas, on lefts as on rights, whereas those on the second and third interdigital areas occur almost twice as frequently on rights. Right hands manifest more transverse ridges than do lefts.

Six comparisons may be made between the two hands of a pair of twins, two bilateral, two heterolateral, and two homolateral. All three types of comparisons in monozygotic twins, and the bilateral similarities in dizygotic twins, show comparably high degrees of similarity, whereas the homolateral and heterolateral similarities of dizygotic twins tend to be considerably less. Homolateral similarities in monozygotic twins are usually greater than bilateral and heterolateral similarities, due to bilateral variations. All four hands may sometimes, of course, be alike with respect to the presence or absence of patterns on the direction of palmar ridges. Striking heterolateral similarity (mirror imaging) is sometimes encountered in monozygotic twins, but not as frequently as is commonly supposed. Monozygotic twins manifest as much bilateral asymmetry as do the single born (MacArthur, 1938; Meyer-Heydenhagen, 1934).

## HERITABILITY

Like most morphological variations, dermatoglyphic configurations are the end products of the interaction of a number of factors. Thus finger prints depend upon the type of patterns (loop, whorl, or arch), as well as upon the size and the angle of the patterns. Ridge counts provide a means of estimating the pattern intensity. Palmar dermatoglyphic configurations depend upon the frequency and types of patterns in the five palmar areas, and the transverseness of the ridges.

Extensive family data have been collected by numerous investigators, including Bonnevie, Weninger, Weinand, and Elderton. The most extensive and thorough investigation was made by Bonnevie on the inheritance of ridge counts on finger tips. Higher ridge counts are negatively correlated with epidermal thickness on pattern areas. Bonnevie postulated one pair of alleles (Vv) lacking dominance as being responsible for variations in epidermal thickness on all digits, and two other pairs of alleles (Uu and Rr) as modifying ridge counts on ulnar and radial digits respectively. Recent work by Holt (1952) and other investigators supports Bonnevie's belief that at least one pair of alleles lacking dominance and having an effect on the epidermal thickness of all digits is important in the determination of the number of ridges. Pattern types (whorls, loops, and arches) are related to the number of ridges, arches lacking ridge counts, whereas whorls are characterized by the highest ridge counts. Here, too, family data clearly indicate lack of dominance, although the number of alleles concerned is not known.

Weninger (1935) obtained family data strongly indicating that patterns in the thenar/first interdigital area are due to a dominant gene with incomplete penetrance. An investigation now under way at Ohio State University indicates that patterns in the second interdigital area are conditioned by a dominant gene with relatively high penetrance. I wish to emphasize, however, that dermatoglyphic configurations are essentially quantitative variations, involving multiple genes. Although the effects of some genes appear to be restricted to certain areas, there are significant correlations in the occurrence of patterns in various areas pointing to the operation of pleiotropic genes. Figure 1 illustrates these interrelationships, as well as relationships between skin pigmentation and handedness with hand patterns.

Note that a negative correlation exists between patterns in the hypothenar and the thenar/first interdigital areas, whereas patterns in the latter area are positively correlated with those in the second interdigital area. Patterns in the three distal areas (II, III, and IV) are positively correlated with each other, and within some populations correlations exist between pattern intensities on finger tips with those in the second and fourth interdigital areas. It seems likely

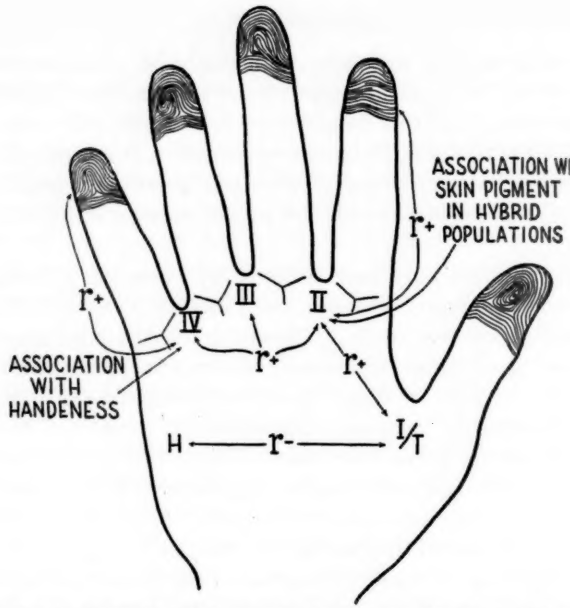


FIG. 1. Genetic interrelationships of finger and palm patterns, skin pigmentation and handedness

that genes affecting pattern intensities on fingers may have some effect on patterns in the distal palmar region.

Family investigations have revealed the types of associations between functional handedness and patterns in the fourth interdigital area resulting from linkage (Rife, 1943). Recent analyses at the Ohio State University of data obtained from mixed populations in the Sudan and also in the United States show associations between skin pigmentation and patterns in the second interdigital area which strongly suggest linkage.

A careful analysis of the hand prints of both monozygotic and dizygotic twins, sibs, and unrelated pairs by MacArthur (1938) showed that ridge counts have the highest heritability of four dermatoglyphic variations, followed in order by patterns on finger tips, palmar patterns, and palmar main lines. Newman, Freeman, and Holzinger (1937) obtained a heritability estimate of approximately 90% for ridge counts in dizygotic twins, an exceptionally high heritability as compared with standard anthropometric variations. Although they did not compute heritabilities for patterns on finger tips and palms, and main line formulae, data from other sources indicate heritabilities averaging well over 50% (MacArthur, 1938; Geipel, 1941).

One may wonder why patterns sometimes occur on only one hand of an individual, or on two of the four hands of a pair of monozygotic twins. While

this problem cannot be considered solved, there is reason to suspect that these bilateral asymmetries may tend to occur in those people who are genotypically heterozygotes or intermediate, or nearer a threshold. That is to say, the genotypic intermediates are more plastic and are thus more responsive to intrauterine influences during early fetal development.

While it would not be difficult to postulate exact modes of inheritance for many variations in dermatoglyphics with as much justification as is frequently employed in postulating the inheritance of other variations in man, I prefer to consider dermatoglyphics as quantitative variations having high heritabilities, which are conditioned by multiple genes. In this respect dermatoglyphics are comparable to pigmentation, which also is known to be highly heritable, and to be influenced by multiple genes. The latter includes pigmentation of hair, eyes, and skin. Some genes are believed to affect only hair, others the eyes, and still others the skin. We know of some genes, however, such as those responsible for albinism, which affect pigmentation in all three areas. Although brown and blues eyes have often been used as an example of simple inheritance, the mode of inheritance is actually quite complex and multiple genes appear to play parts. While dark shades of hair color are known to be epistatic to red, the evidence is conflicting as to whether red pigment is due to one or more dominant genes, or to recessives. I venture to suggest that present day information concerning the genetics of dermatoglyphics is more accurate than that concerning pigmentation, stature, cephalic index, disease resistance, and many inherited abnormalities.

In many respects dermatoglyphics provide a tool or a model of unique importance for human population genetics. Like the blood groups, they are of no apparent assortative importance and are not altered by postnatal environment. Like the usual anthropometric traits, their expression is dependent upon many genes, thus rendering them more stable from one generation to another than blood groups or any other variations due to a single series of alleles. Thus they combine some of the advantages of the blood groups and of anthropometric traits, while lacking obvious disadvantages of each. They would seem to offer rather unique possibilities for investigating the effectiveness of genetic drift in bringing about interpopulation differences in the frequencies of highly heritable, quantitative variations.

## ETHNIC VARIATIONS

Ethnic groups manifest highly significant variations in the occurrence of dermatoglyphic configurations. Like most other genetic traits, the differences are quantitative. I shall briefly discuss variations in finger pattern indices, and patterns on the five palmar areas. Comparable variations have been found for ridge counts on finger tips, direction of palmar main lines, and even toe and sole configurations, but time will not permit me to go into these.

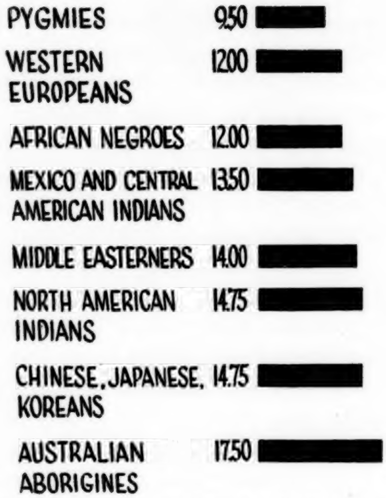


FIG. 2. Finger pattern indices for 8 ethnic groups

First, we shall consider finger pattern indices. The pattern index is that of Cummins, wherein the index of an individual is the sum of loops, plus twice the number of whorls he possesses. Thus an individual with 10 arches has an index of 0, an individual with 10 loops has an index of 10, and one having 10 whorls has an index of 20. Extensive data on pattern indices from people from most parts of the world have recently been compiled. Figure 2 shows the average indices of eight major populations, each of which is an approximation of the average of the indices of several samples. Note that the indices range from a little under 10 among African pygmies to over 17 among Australian aborigines. Also note that the index increases in going from western Europe across to eastern Asia. Among Caucausians, Middle Eastern peoples have significantly higher indices than do western Europeans. African Negroes are characterized by comparatively low indices, similar to those of western Europeans. Middle Easterners have indices similar to those of American Indians.

The occurrence of patterns in the five palmar areas among 5 major ethnic groups is illustrated in figure 3. Let us briefly consider each of these, beginning with the hypothenar area. Note that patterns occur among western Europeans approximately twice as frequently as among Negroes, Mongoloids, and Indians. Middle Easterners manifest slightly higher frequencies than do western Europeans.

Next, let us look at pattern frequencies in the thenar/first interdigital areas. Western Europeans show the lowest, and American Indians the highest frequencies (Steggerda, Steggerda and Lane, 1936). Most remarkable is the great disparity between American Indians and Chinese, who are quite similar with

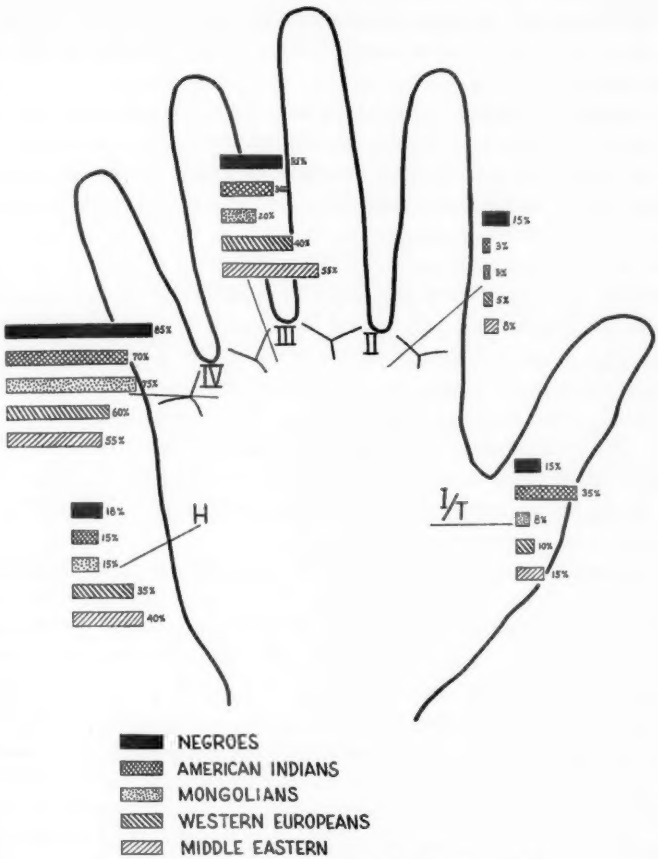


FIG. 3. Ethnic variations in palm pattern frequencies

respect to patterns in other areas, and finger pattern indices. There is good reason to believe that the Indians are descendants of Mongoloids who came across what is now Bering Strait when a land bridge existed there. It seems likely that these wide differences in pattern frequencies in the thenar/first interdigital area may be the result of genetic drift.

The second interdigital area shows relatively high frequencies of patterns among Negroes, and very low ones among Mongoloids and Indians. This area has the lowest frequencies of patterns among all populations, but significant inter-group differences are still quite evident.

The third interdigital area shows highest pattern frequencies among Middle Easterners, followed rather closely by western Europeans. The other three groups are characterized by somewhat lower frequencies.

Patterns occur with greatest frequencies in the fourth interdigital areas. Negroes show 85%, and the lowest incidence is approximately 5%, among Caucasian groups.

To recapitulate: Negroes are characterized by relatively high pattern frequencies in the second and fourth interdigital areas, low frequencies in the hypothenar area, and intermediate frequencies in the thenar/first and third interdigital areas. Mongoloids show high pattern frequencies in the fourth interdigital areas, and low frequencies in each of the others. Both western Europeans and Middle Easterners are characterized by relatively high pattern frequencies in the hypothenar and third interdigital areas, intermediate frequencies in the thenar/first and second interdigital areas, and comparatively low frequencies in the fourth interdigital area. Middle Easterners consistently show higher frequencies in patterns in various areas, as well as higher finger pattern indices than do western Europeans. A review of these charts reveals that each of the major ethnic groups shows significant variations from each of the others with respect to one or more pattern areas, or the finger pattern indices. Hand prints may convey as much information concerning ethnic relationship as do several blood group series.

Twin diagnosis, clarification of disputed paternity, and the determination of ethnic relationships are fundamentally similar problems. In each instance we are concerned with determining degrees of genetic similarity. On the average, the number of genes two individuals have alike depends upon their degree of relationship. It follows that the more closely two ethnic groups are related, the greater will be their similarities in gene frequencies. This principle holds true, regardless of whether we are considering several traits each of which is conditioned by a single set of alleles, or one trait whose expression is determined by several sets of alleles. While it is desirable to know the actual frequencies, lack of such precise knowledge by no means invalidates the employment of quantitative variations, known to be highly heritable. Dermatoglyphics belong in this category. The precision of estimates of relationship depends upon how many genes are involved in the variations under consideration, and their degrees of independence. Striking similarities in the dermatoglyphics of a pair of twins thus provide more positive evidence of monozygosity than does similarity in any blood group series.

Two distantly related ethnic groups might happen to have similar frequencies with respect to a trait determined by a single set of alleles, but the probability of such similarity occurring in a trait whose variation is due to several sets of alleles is greatly reduced. For example, African Negroes and Chinese show somewhat similar frequencies of the ABO blood group genes (Boyd, 1950), but manifest marked differences in their dermatoglyphics.

The value of dermatoglyphics in twin diagnosis is well established. They

have all too frequently been overlooked or neglected in the evaluation of ethnic relationships.

I wish to emphasize that I am not proposing that dermatoglyphics are superior to blood groups and other criteria of relationship, but rather that they provide additional criteria independent of serological variations, pigmentation, skeletal variation, hair form, and other standard criteria, which should add much to the efficiency of evaluation of degrees of ethnic relationship.

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# A Study of the Inheritance of Atopic Hypersensitivity in Man[1]

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## INTRODUCTION

FOR MANY YEARS hereditary predisposition has been suspected as constituting one of the basic factors in the development of atopic hypersensitivity in an individual. It is the purpose of the present work to study more closely the possible genetic mechanisms involved in this condition and to test hypotheses of action of these mechanisms in the various forms of atopy.

Atopic hypersensitivity has been defined in many different ways (Boyd, 1947; Zinsser, Enders, and Fothergill, 1939). Common to all these definitions is the statement that heredity governs predisposition to atopy. Walzer (1948–50) points out that the definition of atopic allergy (hypersensitivity) must be limited as to the type of heredity involved. Other atopic-like conditions in man exist that have an hereditary predisposition, but these forms are not known to have a basic immunological mechanism similar to those for which the term atopy was described (Coca, 1945). From the suggestions of Walzer (1948–50), a definition of atopic hypersensitivity may be formulated for purposes of the present work as a group of allergic diseases that are subject to similar hereditary predispositions and that have similar basic antigen-antibody mechanisms (Boyd, 1947; Campbell et al, 1950; Coca and Grove, 1925a, b; Levine and Coca, 1926; Sherman and Hebold, 1940–41). The antigen is called an atopen and the antibody is termed reagin.

In addition to reagin, an "immune" or blocking antibody has been found to be associated with many atopens (Cooke et al, 1935; Loveless, 1940; Scully and Rackemann, 1940–41). This "immune" type of antibody inhibits the action of the atopen-reagin mechanism. Since the inhibition occurs only in atopic cases which have received desensitization treatment (Loveless, 1940), its presence will not have any adverse effect on hereditary studies.

The history of hereditary studies on atopic hypersensitivity is not very extensive although it began more than thirty years ago. The works of Cooke and VanderVeer (1916), Adkinson (1920), Spain and Cooke (1924), Coca (1926–27), Smith (1928), Balyeat (1928), Bray (1930–31) prompted the state-

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ment of Vaughn (1931) that the "preponderance of evidence indicates that what we inherit is the tendency to become hypersensitive."

Balyeat and Richards (1933) and Bucher and Keeler (1934) showed that atopy is independent of sex. They expressed the belief that the various forms of atopy are due to a pleiotropic effect of a dominant gene that governs hypersensitivity. Wiener, Zieve, and Fries (1935) proposed that the heredity of atopy depends on a single pair of alleles, H and h, where gene h determines the atopic constitution, and gene H, the normal. According to them the expressivity of the genotype is irregular in that about $\frac{1}{6}$ of the heterozygotes are atopic. The homozygous atopic genotype is expressed before puberty. This hypothesis is widely accepted today. Alternative hypotheses are offered and tested herein.

## MATERIALS AND METHODS

A survey was made in a large area of the University Housing Project (University of Notre Dame). This survey was made after an announcement had been published in the official news bulletin of the project that information was sought concerning "allergies." Each family was personally interviewed in the home. Information was obtained concerning exact names and ages of husband, wife, and children, and the localities and durations of residence of each individual particularly during the past ten years.

Each person was classified according to the "presence" or "absence" of atopy. Classification as "presence" was based on the individual's statement of a physician's diagnosis. In a few cases, individuals with "sinus trouble" presented typical symptoms of hay fever, and were classed as "presence." The possession of atopic hypersensitivity of any type at any time during the life of the individual was considered positive evidence for the presence of atopy.

Atopic individuals were further classified as to the form of atopy they possess, such as asthma, hay fever, etc. Information concerning age of onset of symptoms and the causative agents, especially grass pollen and ragweed pollen, was sought from these individuals.

From the survey a selected list of individuals was made. Adults only (husbands and wives) were considered. Selection was based on two factors; first, on the basis of residence in the midwestern area of the United States especially in the last ten years (to insure that the individual was exposed to the common atopic agents of the area for a considerable length of time); second, on the basis of the probability that these members represent a random sample of the population in panmixia of this area (members belonging to racial and religious segregated groups were omitted).

The selected list contained 198 individuals or 99 pairs (husband and wife) of the Housing Project. This sample is used to determine the incidence of atopy and types of atopy in the population represented by the sample. Gene fre-

quencies are calculated from this information for the genetic hypotheses postulated in the results.

Family histories of atopy for pooled mating analysis were obtained from three sources: from students in the biological laboratories at the University, from residents of a small area of the Housing Project not included in the survey sample, and from students in the bacteriological and food laboratories of a nearby college for women. Names were checked to be certain that students giving family histories were not included in the survey sample.

Family histories were obtained from atopic individuals and from non-atopic individuals in whose immediate family (parents and sibs) atopy was present. By use of this collection method, information is obtained on three types of matings; atopic to atopic, atopic to normal, and normal to normal. However, it restricts the normal to normal mating types to those that possess at least one atopic offspring. The other two types are not restricted in this way.

In a personal interview with the student the same information was sought as in the interviews with the members of the survey sample. The questions were extended to include all members of the immediate family. The basis of classification was the same as that used in the survey. Since information concerning relatives outside of the immediate family cannot be considered very accurate, atopic relatives were noted but not included in analyses.

The family histories were selected for use in pooled family data analysis on the same basis as selection for listing in the survey sample. The parents in these family histories range from the forty-five to sixty year age group; the children, from the twelve to thirty year age group, the majority being over eighteen years. Children younger than twelve years were omitted from analysis. The family information given by the residents of the small area of Housing Project (not used in the survey sample) concerned the parents and sibs of residents rather than their children.

Pooled matings are used to analyze the probability of hypotheses of action of genetic mechanisms in the various forms of atopy. The forms considered are general atopy (including all forms), hay fever, asthma, and eczema. Gene frequencies calculated from the random sample data are used to test these probabilities.

## RESULTS

### *The Survey Sample*

It is assumed that the data obtained from students and wives living in the Housing Project represent a random sample for atopic traits in the general population in panmixia of the midwestern area of the United States, since there was no deliberate selection for or against the traits in question in collecting the data.

TABLE 1.—THE OBSERVED NUMBERS OF NORMAL AND ATOPIC MALES AND FEMALES IN THE SURVEY DATA. PROBABILITY VALUES ARE DETERMINED BY CHI SQUARE METHOD

| | Males | Females | Total | P value |
|---|---|---|---|---|
| General Atopy | | | | |
| Atopic | 19 | 21 | 40 | |
| Normal | 80 | 78 | 158 | |
| Total | 99 | 99 | 198 | 0.80 |
| Hay Fever | | | | |
| Atopic | 13 | 19 | 32 | |
| Normal | 86 | 80 | 166 | |
| Total | 99 | 99 | 198 | 0.30 |
| Atopic Asthma | | | | |
| Atopic | 6 | 8 | 14 | |
| Normal | 93 | 91 | 184 | |
| Total | 99 | 99 | 198 | 0.60 |
| Atopic Eczema | | | | |
| Atopic | 2 | 3 | 5 | |
| Normal | 97 | 96 | 193 | |
| Total | 99 | 99 | 198 | 0.60 |

Before the sample is used in genetic analysis for atopic traits, statistical tests are made to determine whether or not there is any significantly irregular association between sex and the various forms of atopy. First, considering atopy in general, all individuals of the survey sample are classified as to sex and as to presence or absence of atopy *in any form*. Second, all individuals of the survey sample are classified as to sex and as to the presence or absence of hay fever; third, all individuals are classified as to sex and as to the presence or absence of asthma; and fourth, as to sex and as to the presence or absence of eczema. The entire sample is entered in table 1 four times, and in each case those not possessing the specific type atopy in question are considered normal for that type.

The observed numbers of each class are compared to the numbers expected in a random distribution of sex and atopy or forms of atopy and the Chi square method is used to determine the probability values in table 1.

The Chi square values, based on one degree of freedom, indicate that there is a random distribution of sex and traits. The term "atopic" is used to design nate individuals possessing the condition noted in the heading of each block in the table.

The tabulated results on the distribution of atopic traits in the selected survey sample are presented in table 2. Again the entire sample is entered into the table four times and in each case individuals not possessing the specific type atopy are considered normal.

TABLE 2.—TABULATION OF SURVEY RESULTS OF 198 INDIVIDUALS

| Survey Members | Affected Members | Normal Members | Total Members |
|---|---|---|---|
| General Atopy | | | |
| Number | 40 | 158 | 198 |
| Per cent | 20.20 | 79.80 | 100 |
| Hay Fever | | | |
| Number | 32 | 166 | 198 |
| Per cent | 16.16 | 83.84 | 100 |
| Asthma | | | |
| Number | 14 | 184 | 198 |
| Per cent | 7.07 | 92.93 | 100 |
| Eczema | | | |
| Number | 5 | 193 | 198 |
| Per cent | 2.53 | 97.47 | 100 |

All percentages are based on the number of individuals in the whole selected sample. These results may be used to calculate gene frequencies for the traits in the population represented by the sample. The frequencies will be a function of the hypotheses to be tested.

### *The Proposed Hypotheses*

Before considering the genetic hypothesis suggested by Wiener et al. (1935), a simpler hypothesis for general atopy is postulated. Let it be assumed for the first hypothesis that the predisposition to general atopy is governed by a recessive gene, and the normal state by its dominant allele. The homozygous recessive genotype can be recognized as atopic individuals, while normal individuals will possess the heterozygous or homozygous dominant genotype. The frequency of the three genotypes will occur in the proportion $p^2 : 2pq : q^2$ in the population (Hardy-Weinberg principle) where $p$ represents the frequency of the dominant allele and $q$ the frequency of its recessive allele. An estimate of the recessive allele frequency in the population is calculated from the survey sample as the square root of the proportion of the recessive genotypes, recognized phenotypically as atopic individuals. This frequency is estimated to be $\sqrt{0.2020}$ or 0.4494. The frequency of the dominant allele, 0.5506, is calculated by subtracting 0.4494 from unity.

However, the hypothesis of Wiener et al. (1935) contends that the predisposition to atopy is governed by an irregular recessive gene. The irregularity is expressed by the suggestion that one sixth of the heterozygotes are phenotypically similar to the homozygous recessive genotype. The genetic equilibrium expression $p^2 + 2pq + q^2 = 1$ must then be altered (again assigning symbols

$p$ and $q$ to represent the frequencies of the dominant and recessive alleles respectively). The normal phenotype is represented by the proportion $p^2 + 2pq - \frac{1}{6}(2pq)$, the atopic phenotype by the proportion $q^2 + \frac{1}{6}(2pq)$, where $p^2 + (2pq - \frac{1}{3}pq) + (q^2 + \frac{1}{3}pq)$ equals one. The atopic individuals represent 20.20% of the sample, therefore, $q^2 + \frac{1}{3}pq$ has the numerical value 0.2020. This may be solved for $q$ as follows.

Let $$a = p^2 + (2pq - 1/3pq)$$

$$p = -5/6q + 1/2\sqrt{\frac{25q^2}{9} + 4a}$$

let $$b = q^2 + 1/3pq$$

$$o = q^2 + 1/3q\left(-5/6q \pm 1/2\sqrt{\frac{25q^2}{9} + 4a}\right) - b$$

squaring, transposing, we get

$$q^2 = \frac{\frac{13b + a}{9} \pm \sqrt{\left(\frac{13b + a}{9}\right)^2 - \frac{16}{9}b^2}}{\frac{8}{9}}$$

where $$a = 0.7980 \text{ and } b = 0.2020$$
$$q = 0.3550$$
$$p = 1 - 0.3550 = 0.6450$$

According to calculations using Wiener's hypothesis, 35.50% of the genes in the population at the atopic allele loci are recessive.

The explanations for the irregularity in the heterozygote could be numerous both genetically and environmentally. Genetically, it may be that atopic predisposition is governed by several closely linked genes, multiple alleles, modifiers, or penetrance, etc. These explanations suggest new hypotheses for testing.

A third hypothesis is offered here, that each form of atopy is completely independent of the others and each has its own basic genetic mechanism. In this hypothesis, a recessive allele "$a$" predisposes the nasal tissue to hay fever; a recessive allele "$b$" predisposes the bronchiolar tissue to asthma; a recessive allele "$c$" predisposes the skin to eczema. In other words, genes govern the sites affected rather than govern general predisposition. Whether or not these genes are linked will not affect the analyses to be made.

On the basis of this third hypothesis, the allele frequencies are calculated from the survey sample for the three forms of atopy using the type of analysis as described in the first hypothesis. The results are presented in table 3.

These frequencies will be used in analysis of pooled family data to predict

TABLE 3.—CALCULATED ALLELE, FREQUENCIES FOR ASTHMA, HAY FEVER, AND ECZEMA

| Frequency | Hay Fever | Asthma | Eczema |
|---|---|---|---|
| $p$ | 0.5980 | 0.7341 | 0.8409 |
| $q$ | 0.4020 | 0.2659 | 0.1591 |

the expected number of types of matings and the proportion of recessive offspring in certain matings. No analysis for migraine has been attempted because of the very small number of cases in the data.

### *Family Histories*

Snyder (1947) presents a method of analyzing family histories for an inherited trait. This method is applicable to an inherited trait that is dependent upon a single pair of autosomal alleles one of which is completely dominant to the other. The procedure of this method consists of a study of the proportion of recessive children produced by random matings of dominant to dominant and dominant to recessive. It is essential to this procedure that the family histories obtained for the traits represent random matings in the population. Thus a statistical test is necessary to determine whether the family data included in this study actually fulfill this condition. The details of the test are described below.

### *Analysis for Random Matings*

The collected family histories for general atopy, for hay fever, asthma, and eczema are classified as to types of mating. Depending upon the genetic hypotheses postulated previously, each history is either dominant to dominant, dominant to recessive, or recessive to recessive type of mating for each trait to be considered.

The proportion of mating types expected in the population can be calculated from the allele frequencies obtained from the survey sample. Since family histories are believed to be representative of the same population as the survey sample, the expected proportions can be compared to the observed proportions in the pooled family data.

Since all of the genetic hypotheses, except Wiener's hypothesis, concern a recessive genotype for presence of a trait, the method for calculating mating type proportions will be similar. In such hereditary traits there are three possible phenotypic matings, normal to normal, normal to atopic, and atopic to atopic.

The expected proportions of normal to normal matings are calculated as the sum of the expected proportions of the constituent genotypic matings, $AA \times AA$, $AA \times Aa$, and $Aa \times Aa$ ($A$ represents the dominant gene, $a$ the recessive). Since the dominant homozygous genotype appears in the popu-

TABLE 4.—EXPECTED PROPORTIONS OF PHENOTYPIC MATING TYPES IN THE POPULATION

| Phenotypic Mating Types | Proportions in $p$ and $q$ |
|---|---|
| Normal × Normal | $p^4 + 4\,p^3q + 4\,p^2q^2$ |
| Normal × Atopic | $2\,p^2q^2 + 4\,pq^3$ |
| Atopic × Atopic | $q^4$ |
| Total | $p^4 + 4\,p^3q + 6\,p^2q^2 + 4\,pq^3 + q^4 = 1$ |

TABLE 5.—NUMERICAL PROPORTIONS OF PHENOTYPIC MATING TYPES EXPECTED IN THE POPULATION AS CALCULATED FROM THE GENE FREQUENCIES OF THE SURVEY SAMPLE

| Atopic Forms | Normal with Normal | Normal with Atopic | Atopic with Atopic | Total Proportions |
|---|---|---|---|---|
| General Atopy | 0.6369 | 0.3223 | 0.0408 | 1.0000 |
| Hay Fever | 0.7030 | 0.2710 | 0.0260 | 1.0000 |
| Asthma | 0.8637 | 0.1314 | 0.0049 | 1.0000 |
| Eczema | 0.9500 | 0.0493 | 0.0007 | 1.0000 |

lation in the proportion $p^2$, and the heterozygote in the proportion $2pq$, the proportions of $AA \times AA$ matings will be $p^4$, that of $AA \times Aa$ will be $4p^3q$, that of $Aa \times Aa$ will be $4p^2q^2$. The expected proportions of normal to atopic matings are calculated as the sum of the expected proportions of the constituent genotypic matings; $AA \times aa$, the proportion $2p^2q^2$; and $Aa \times aa$, the proportion $4pq^3$. The atopic to atopic matings will be expected in the proportion $q^4$. Table 4 presents tabulation of these expected results in terms of allele frequencies $p$ and $q$.

The allele frequencies for each form of atopy that were obtained from the random sample are substituted for $p$ and $q$ in the algebraic proportion values of table 4. These numerical proportions of the phenotypic mating types for each form of atopy expected in the population for the recessive hypotheses are presented in table 5.

There is no obvious reason to suspect that the pooled family data include mating types of normal with atopic, and atopic with atopic that do not represent random mating types for the atopic trait in the population. However, as stated previously, the method of selection for family history collection presents a serious bias to the information on normal to normal matings since the selection restricted this type to those having at least one atopic offspring. This bias[3] can be corrected if it be assumed that each individual in the laboratories who did not give a family history, had non-atopic parents and sibs.

The observed total number of normal with normal mating types is computed

[3] It is believed that the method of interviewing gave everyone an equally private opportunity for discussing the presence of atopy in their immediate family. From the nature of the response, the inquirer did not feel that any individual contacted had any reason to conceal information on atopy in the family.

TABLE 6.—COMPARISON OF OBSERVED WITH EXPECTED NUMBER OF MATING TYPES IN THE FAMILY DATA

| Conditions | Types of Matings | Observed | Expected | Probability |
|---|---|---|---|---|
| Considering only General Atopy | $A- \times A-$ | 142.0 | 143.9 | |
| | $A- \times aa$ | 75.0 | 72.9 | |
| | $aa \times aa$ | 9.0 | 9.2 | |
| | Total | 226.0 | 226.0 | 0.95 |
| Considering only Hay Fever | $A- \times A-$ | 158.0 | 158.9 | |
| | $A- \times aa$ | 63.0 | 61.2 | |
| | $aa \times aa$ | 5.0 | 5.9 | |
| | Total | 226.0 | 226.0 | 0.90 |
| Considering only Atopic Asthma | $A- \times A-$ | 205.0 | 195.2 | |
| | $A- \times aa$ | 21.0 | 29.7 | |
| | $aa \times aa$ | 0.0 | 1.1 | |
| | Total | 226.0 | 226.0 | 0.10 |
| Considering only Atopic Eczema | $A- \times A-$ | 215.0 | 214.72 | |
| | $A- \times aa$ | 10.0 | 11.12 | |
| | $aa \times aa$ | 1.0 | 0.16 | |
| | Total | 226.0 | 226.00 | 0.30 |

as the number of such matings in the pooled family data plus the number of matings represented by individuals not giving family histories. The number of normal with atopic and atopic with atopic are taken from the pooled family data. The observed number of each phenotypic mating type for general atopy and for asthma, eczema, and hay fever, is presented in table 6 in which the symbol $A-$ is used to indicate a normal parent and $aa$ to indicate an atopic parent. The total 226 matings are entered into the table four times, in each case individuals not possessing the specific type of hypersensitivity in question are considered normal for that type.

The numerical proportions of mating types are applied to the data to determine the expected number of matings for each form of atopy in the family data. The Chi square test is used to determine the significance of the deviation.

The P values indicate that there is no significant departure of observed from the expected number of mating types. Thus it is probable that the pooled matings represent for each trait a random sample of the population from which the matings and the survey data were obtained according to the methods used.

### *Analysis of Random Normal to Atopic Matings*

Snyder (1947) has shown that in random matings of dominant with recessive, the proportion of recessive offspring is determined by the formula

$$\frac{q}{1+q}$$

TABLE 7.—EXPECTED PROPORTIONS OF RECESSIVE CHILDREN FROM MATINGS OF DOMINANTS WITH RECESSIVES IN THE FAMILY DATA

| | General Atopy | Hay Fever | Atopic Asthma | Atopic Eczema |
|---|---|---|---|---|
| $\frac{q}{1+q}$ | 0.3100 | 0.2868 | 0.2100 | 0.1373 |
| observed proportions | 0.4600 | 0.3190 | 0.1230 | 0.1429 |
| deviation | 0.1500 | 0.0322 | 0.0870 | 0.0056 |
| $\frac{\text{deviation}}{\text{S.E.}}$ | 8.4× | 1.92× | 1.30× | 1.90× |

where $q$ is the frequency of the proposed recessive allele. This presents an easy method by which one may determine which of the recessive gene hypotheses is most likely. Substituting the proper numerical values obtained from the survey sample, into the formula, the expected proportions of recessive children in the family data are calculated. The observed proportions in the family data are compared with the expected in table 7. The significance is determined by comparing the standard error with the deviation obtained. The standard error is computed from the formula given by Snyder (1947).

$$\text{Standard error} \qquad \frac{q}{1+q} = \frac{1-q}{2(1+q)}\sqrt{\frac{1}{N(1-q^2)}}$$

Data on only one of the four categories tested show a deviation greater than twice the standard error.

### *Analysis of Heterozygous Matings*

In dominant to dominant matings, only family histories with at least one atopic member were investigated. According to all recessive hypotheses proposed, the matings will consist of only one genotypic mating type, the heterozygote with the heterzygote.

Stern (1949) and Snyder (1946) present a method (described by Hogben, 1932) of testing the recessive hypotheses in cases where normal matings are selected on the basis of possessing at least one recessive offspring. The method is based on correction of the three normal to one affected ratio expected from heterozygous parents for sibships of various sizes. The method consists of a correction in ratio by determining the theoretical population of offspring of heterozygous parents. Snyder (1946) also gives a method for determining the standard error. The ratio between the normal to normal matings of a given sibship size (producing at least one affected offspring) and the normal to normal matings of the same sibship size (having only normal offspring) is constant. This constant is used to determine the theoretical population and the standard

TABLE 8.—ANALYSIS FOR GENERAL ATOPY. NORMAL WITH NORMAL MATINGS PRODUCING AT LEAST ONE AFFECTED OFFSPRING

| S | Ns | SNs | r | CsNs | KsNs |
|---|---|---|---|---|---|
| 1 | 5 | 5 | 5 | 20.0000 | 0.0000 |
| 2 | 14 | 28 | 18 | 63.9996 | 1.7143 |
| 3 | 19 | 57 | 34 | 98.5948 | 4.9964 |
| 4 | 11 | 44 | 19 | 64.3654 | 4.6205 |
| 5 | 7 | 35 | 12 | 45.8899 | 4.1425 |
| 6 | 5 | 30 | 15 | 36.4955 | 3.8797 |
| 7 | 3 | 21 | 6 | 24.3429 | 2.9107 |
| 8 | 3 | 24 | 7 | 26.6700 | 3.5172 |
| 9 | 1 | 9 | 5 | 9.7306 | 1.3802 |
| 10 | 1 | 10 | 2 | 10.5970 | 1.5917 |
| Total............ | 69 | 263 | 123 | 400.5777 | 28.7533 |

$$\text{Standard Error} = \sqrt{\frac{\text{KsNs Total}}{\text{CsNs Total}}} = \sqrt{\frac{28.7533}{400.5777}} = 0.0130$$

$$0.0130 \times 200 = 2.60\%$$

$$\text{Per cent r} = \frac{\text{r} \times 100}{\text{CsNs Total}} = \frac{123 \times 100}{400.5777} = 30.71\%$$

$$30.7\% - 25.00\% = 5.71\%$$

Abbreviations:
S = Size of Sibship
Ns = Number of Such Sibship
SNs = Total Number of Children
r = Total Number of Recessives
Cs = Theoretical Population Constant
Ks = Standard Deviation Constant

deviation of that population. Tables of these constants are presented by Hogben (1932).

Considering general atopy and its various forms, matings of non-atopic parents with at least one affected offspring are pooled according to the size of sibship. The number of each size sibship, the total number of children in each, and the number of atopic offspring are placed in tables 8 through 11. The theoretical population and the standard deviation are calculated.

The deviations obtained are greater than twice the standard error in analysis for general atopy (table 8). This indicates that general atopy is not genetically governed according to the first hypothesis herein proposed.

The analyses for hay fever, asthma, and eczema lend evidence to support the proposed hypotheses that each condition is governed by a recessive allele of a single gene pair. The deviations of the observed proportions is less than twice the standard error in each case; for hay fever the deviation is 2.73 and 2 S.E. is 2.76; for asthma the deviation is 3.19 and 2 S.E. is 3.68; for eczema the deviation is 0.17 and 2 S.E. is 4.08.

TABLE 9.—ANALYSIS FOR ATOPIC HAY FEVER. NORMAL WITH NORMAL MATINGS PRODUCING AT LEAST ONE AFFECTED OFFSPRING

| S | Ns | SNs | r | CsNs | KsNs |
|---|---|---|---|---|---|
| 1 | 4 | 4 | 4 | 16.0000 | 0.0000 |
| 2 | 15 | 30 | 16 | 68.5710 | 1.8367 |
| 3 | 18 | 54 | 26 | 93.4056 | 4.7334 |
| 4 | 8 | 32 | 12 | 46.8612 | 3.3604 |
| 5 | 8 | 40 | 14 | 52.4456 | 7.7342 |
| 6 | 5 | 30 | 12 | 36.4955 | 3.8697 |
| 7 | 2 | 14 | 4 | 16.1566 | 1.9404 |
| 8 | 4 | 32 | 13 | 35.5600 | 4.6896 |
| 9 | 1 | 9 | 4 | 9.7306 | 1.3802 |
| 10 | 1 | 10 | 2 | 10.5970 | 1.5917 |
| Total............ | 66 | 255 | 107 | 385.8231 | 28.1466 |

$$\text{Standard Error} = \sqrt{\frac{\text{KsNs Total}}{\text{CsNs Total}}} = \sqrt{\frac{28.1466}{385.8231}} = 0.0138$$

$$0.0138 \times 200 = 2.76\%$$

$$\text{Per cent r} = \frac{\text{r} \times 100}{\text{CsNs Total}} = \frac{107 \times 100}{385.8231} = 27.73\%$$

$$27.73\% - 25.00\% = 2.73\%$$

Abbreviations

The same symbols are used as in Table 8.

## DISCUSSION

Walzer (1948–50) points out that heredity may influence the sites affected in the expression of atopy. Hay fever, atopic asthma, and eczema are atopic reactions at different sites in an individual. This implies that certain tissues are more susceptible than others to the metabolic products of an atopen-reagin reaction in the tissues of an atopic individual.

An hypothesis is postulated, that three distinct pairs of alleles govern tissue site susceptibility. In hay fever the recessive allele of one gene pair allows the tissues of the nasal passages to react to the toxic products of the atopen-reagin reaction. For atopic asthma the recessive member of second gene pair allows a similar susceptibility to the tissues of the bronchioles. For eczema, the recessive member of a third gene pair allows the same type of susceptibility to the tissues of the skin.

Analysis of the data obtained indicates first, that the atopic predisposition to the sites affected is randomly associated with sex; second, that the proportion of mating types (for hay fever, asthma, and eczema) in the family data corresponds to the proportion predicted for a random sample of the popu-

TABLE 10.—ANALYSIS FOR ATOPIC ASTHMA. NORMAL WITH NORMAL MATINGS PRODUCING AT LEAST ONE AFFECTED OFFSPRING

| S | Ns | SNs | r | CsNs | KsNs |
|---|---|---|---|---|---|
| 1 | 4 | 4 | 4 | 16.0000 | 0.0000 |
| 2 | 8 | 16 | 9 | 36.5712 | 0.9796 |
| 3 | 8 | 24 | 9 | 41.5136 | 2.1038 |
| 4 | 6 | 24 | 9 | 35.1084 | 2.5203 |
| 5 | 4 | 20 | 5 | 26.2228 | 2.3671 |
| 6 | 2 | 12 | 4 | 14.5982 | 1.5519 |
| 7 | 1 | 7 | 1 | 8.0783 | 0.9702 |
| 8 | 1 | 8 | 1 | 8.8900 | 1.1724 |
| 9 | 1 | 9 | 1 | 9.7306 | 1.3802 |
| Total............ | 35 | 124 | 43 | 196.7131 | 13.0455 |

$$\text{Standard Error} = \sqrt{\frac{\text{KsNs Total}}{\text{CsNs Total}}} = \sqrt{\frac{13.0455}{196.7131}} = 0.0184$$

$$0.0184 \times 200 = 3.68\%$$

$$\text{Per cent r} = \frac{\text{r} \times 100}{\text{CsNs Total}} = \frac{43 \times 100}{196.7131} = 21.81\%$$

$$25.00\% - 21.81\% = 3.19\%$$

Abbreviations
The same symbols are used as in Table 8.

lation on the basis of calculations using the allele frequencies from the survey sample (considering separately the gene pairs for affected sites); and third, analyses of the random normal to atopic (hay fever, asthma, and eczema) matings for the proportion of recessive children supports the recessive gene hypotheses for hay fever, asthma, and eczema since the deviations are less than twice the standard error. Fourth, the more critical type of analyses (analyses of the heterozygote matings) for hay fever, asthma, and eczema reveals non-significant deviations between the observed and expected numbers of recessive offspring.

All of the observed facts give strong evidence to the hypothesis that three recessive alleles, each a member of a separate gene pair govern the predisposition to the sites affected in atopic individuals. This implies that genic action operates in the susceptibility of the tissues concerned to the stimulating effects of the metabolic products of the atopen-reagin reactions.

Wiener et al. (1935) present statistical data to test their hypothesis that hereditary predisposition to atopy is governed by an irregular recessive gene. The critical method used by these authors is the same as one used in this work.

The hypothesis of an irregular recessive gene is not readily tested by the data

TABLE 11.—ANALYSIS FOR ECZEMA. NORMAL WITH NORMAL MATINGS PRODUCING AT LEAST ONE AFFECTED OFFSPRING

| S | Ns | SNs | r | CsNs | KsNs |
|---|---|---|---|---|---|
| 1 | 4 | 4 | 4 | 16.0000 | 0.0000 |
| 2 | 6 | 12 | 7 | 27.4284 | 0.7347 |
| 3 | 4 | 12 | 6 | 20.7568 | 1.0519 |
| 4 | 5 | 20 | 8 | 29.2570 | 2.1003 |
| 5 | 5 | 25 | 6 | 32.7785 | 2.9589 |
| 6 | 3 | 18 | 5 | 21.8973 | 2.3278 |
| 7 | 1 | 7 | 2 | 8.0783 | 0.9702 |
| 8 | 1 | 8 | 3 | 8.8900 | 1.1724 |
| Total............. | 29 | 106 | 41 | 165.0863 | 11.3162 |

$$\text{Standard Error} = \sqrt{\frac{\text{KsNs Total}}{\text{CsNs Total}}} = \sqrt{\frac{11.3162}{165.0863}} = 0.0204$$

$$0.0204 \times 200 = 4.08\%$$

$$\text{Per cent r} = \frac{\text{r} \times 100}{\text{CsNs Total}} = \frac{41 \times 100}{165.0863} = 24.83\%$$

$$25.00\% - 24.83\% = 0.17\%$$

Abbreviations
The same symbols are used as in Table 8.

for general atopy presented in the results because the age of onset of symptoms is not definitely known for the parents in the matings. However, the allele frequencies given by the above authors are comparable to those calculated with the survey data. These authors report that seven per cent of the population are atopic. (The estimate of seven per cent was computed from the literature cited by them.) They calculated a gene frequency for the recessive gene to be about fifteen per cent. In the present work about twenty per cent of the survey was classified as atopic, and the gene frequency based on Wiener's hypothesis is approximately thirty-five per cent.

In Wiener's hypothesis, the homozygous recessive genotype is believed to permit the expression of atopy before puberty. This apparent effect may be due to the earlier age of onset for the expression of one of the affected site genotypes. Eczema seems to be more prevalent in children than asthma and hay fever. However, a condition of this type would be masked when all forms of atopy are considered as a single phenomenon. Data confirming this have not been found in the literature. All individuals with eczema in the survey sample have an age of onset before puberty. The majority with hay fever and asthma had the age of onset after puberty.

The data on general atopy, especially in pooled mating analysis, failed to give results consistent with a single recessive gene hypothesis. Analysis of

heterozygous matings for the proportion of recessive offspring present a deviation much greater than twice the standard error. It may be pointed out that the analysis for general atopy usually contained more atopic individuals than were expected according to the single recessive gene hypothesis.

## ACKNOWLEDGMENTS

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## SUMMARY

1. A survey, believed to represent a random sample of the general population in panmixia of the midwestern area of the United States, was made to determine the frequency of occurrence of atopy and the various forms thereof. Family histories of atopy which are believed to represent the same population were obtained to ascertain the plausibility of certain genetic hypotheses.

2. The data indicate that there is a random association of sex and atopy or its various forms, asthma, hay fever, and eczema.

3. Gene frequencies, calculated from the survey sample, were used in analyses of pooled family data. The results give strong evidence that distinct gene pairs govern the susceptibility of tissues to the atopic hypersensitivity reaction. Hay fever susceptibility is governed by a recessive allele of one gene pair, atopic asthma susceptibility, by a recessive allele of a second gene pair, and eczema susceptibility, by a recessive allele of a third gene pair.

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# Coincidence of Huntington's Chorea and Multiple Neurofibromatosis in Two Generations

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STUDIES OF HEREDITARY CHARACTERISTICS in humans rarely report the coincidence of two rather rare, dominant, and deleterious genes within the same family strain. For this reason, and because our proposita represents the first appearance of the mutation for one of the characteristics, we wish to report such an observation.

Figure 1 presents an abbreviated pedigree chart indicating the development in the proposita (16) of multiple neurofibromatosis (von Recklinghausen's disease) in addition to Huntington's chorea with which her mother, grandfather, and four of her eight siblings were known to be afflicted. As may be seen, both conditions were transmitted to her two children who were mentally deficient in addition. A granddaughter (78) at age three shows no symptoms of Huntington's chorea or neurofibromatosis but appears to be mentally deficient (I.Q. 64). The father of this child has an I.Q. of 121 on the Performance Scale of the Wechsler-Bellevue Test, Form II.

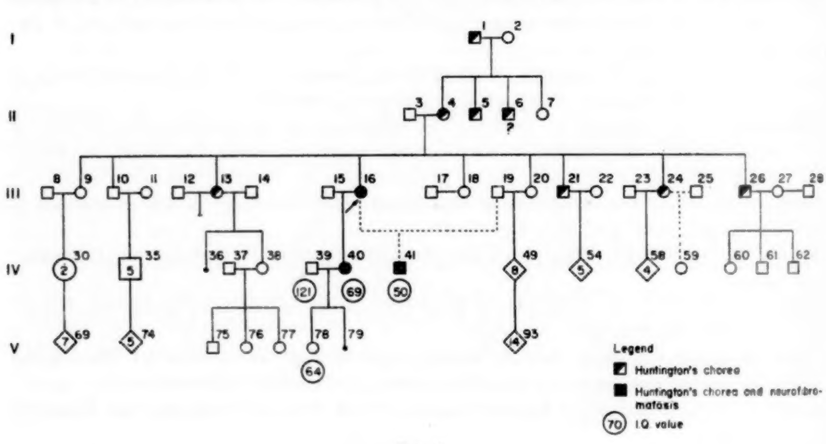


FIG. 1

The diagnosis of Huntington's chorea has been clearly established—five

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members of the family including the proposita, her mother, and her son have been admitted to the Rochester State Hospital with this condition. None of these with the exception of the proposita and her son has shown any evidence of abnormalities suggestive of neurofibromatosis. Her father died at age eighty of pneumonia and is said to have been otherwise normal. Her mother was a patient in the Rochester State Hospital for one year, where she died at the age of fifty. If she had had neurofibromatosis it would certainly have been observed. Von Recklinghausen's disease was diagnosed on the basis of clinical examination in (16) while histopathological studies from biopsy confirmed the diagnosis in (40) and (41). It thus appears that our proposita developed this condition as a result of a gene mutation which occurred in either her father or mother and was transmitted to her.

The question of mental deficiency in this family is also of interest. Frequently cited as a concomitant of neurofibromatosis, mental deficiency appears for the first time in this pedigree in cases (41) (I.Q. 50) and (40) (I.Q. 69). The proposita, her siblings, her parents, and all other known relatives have possessed at least low average intelligence judging from educational and socio-economic status.

## SUMMARY

A pedigree is presented in which Huntington's chorea has been traced for four generations. One affected individual also developed multiple neurofibromatosis (von Recklinghausen's disease) apparently as a result of a mutation in one or the other of her parents, and both of these conditions were transmitted to her two children. These two children were also mentally deficient, and the daughter of one appears at age three to be so while all other members of the family appear to be of at least low average intelligence.

# The Use of the Sequential Analysis Method in Problems in Human Genetics[1]

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THE PROBLEM which confronts the investigator of certain aspects of human heredity is one common to many fields of research, namely, how large a sample is necessary to give an answer that is statistically valid within the limits set by the investigator. If the process of collecting data is expensive, either in time or money, it is desirable to come to a conclusion with as little waste as is compatible with accuracy. Even if the process is not expensive, it is still worth while to reach the end as soon as possible, and to turn one's energies into new channels. The method of sequential analysis is designed to achieve these ends.[2] It furnishes an answer with the least possible number of cases.

It is not intended here to review the development of the method. The original texts (1, 2) must be consulted for the ideas and the formulas which are used. All that I intend here is to show how sequential analysis has been utilized in a problem in human inheritance. The aspect of the method dealing with the comparison of two objects or items of information derived from two procedures, hence the one described as a "double dichotomy", is the one utilized here. One must determine how large a sample of items acquired by the two procedures must be compared in order that the investigator may have a reasonable assurance that his conclusions in favor of one or the other procedure are justified.

I am applying the sequential analysis method to data on the incidence of breast cancer in two populations, to determine whether there is significantly more breast cancer among the female relatives of women who have breast cancer (Population 1 ($P_1$)) than there is among the female relatives of women who have not developed breast cancer (Population 0 ($P_0$)); also whether there is more cancer in general in the males of $P_1$ than in the males of $P_0$. Relatives from $P_0$ will be compared with similar relatives from $P_1$, taking care to match living relatives only with living; dead with dead; and matching them for sex, age and type of relationship. Paternal aunts will be compared only with paternal aunts, maternal aunts only with maternal aunts, etc. The incidence of

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[2] I desire to express my thanks to Professor Earl L. Green of the Zoology Department for calling my attention to the sequential analysis method; and to Professor Ransom Whitney of the Mathematics Department for reading this paper and offering many helpful suggestions.

breast cancer in the two populations may be the same or it may be different, with the degree of dissimilarity being small, large, or some intermediate value. If the amount of breast cancer in $P_1$ is, for example, only 1.1 times that in $P_0$, the difference is immaterial from the standpoint of prevention, early detection, etc. Of what magnitude must the difference be before I will consider it of sufficient importance to call it a real difference? I have arbitrarily chosen the value of 3 as one which would constitute a difference of practical importance.

Two hypotheses are then formulated; one, $H_0$, that there is no difference in the incidence of breast cancer in $P_1$ and $P_0$: the other, $H_1$, that there is at least 3 times as much breast cancer in $P_1$ as in $P_0$. The proportion of breast cancer patients in the general population is about 4 in 100. We assume that the proportion in our population $P_0$ is the same. This proportion will be represented as $p_0$. The corresponding proportion in the population $P_1$ which will be looked for is 12 in 100. The ratio of 12:4 is the value 3 which I have chosen. These values will appear in the formulas to be given later on.

## METHOD OF MATCHING RELATIVES AT RANDOM

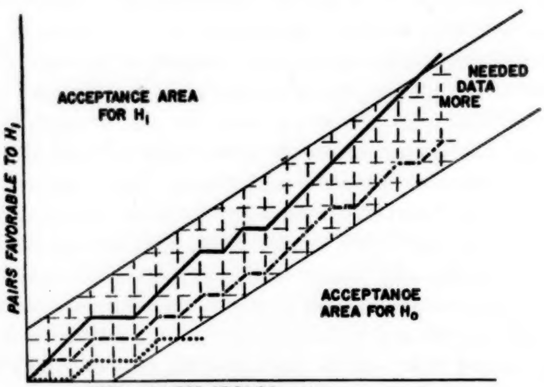
It is essential that the matching be done at random as nearly as possible. The manner in which this is accomplished in my problem of inheritance in breast cancer is achieved as follows:

As soon as the complete information is received on any one relative, whether in the control population $P_0$, or in the "experimental" population $P_1$, a card 3 x 5 is made out with skeleton information on it concerning the essential facts about the relative. This information consists of the name of the person, his file number in the project, his relationship to the "patient" who was the first person interviewed, his age, and if dead, the year of death. If the relative had cancer, this fact is entered on the card, together with the organ which was affected. All relatives of women with breast cancer are recorded on blue cards; all relatives of "control" women are listed on yellow cards. A second population listed on pink cards is also used, namely, the relatives of any patient, male or female, with cancer of an organ other than the breast. Starting with a blue card, containing, for example, the name of a patient's mother who died in 1930 at the age of 67, the first pink card which is found for a mother dying around 1930, and at the age of 67, plus or minus 1 year, is selected as the matching card. Similarly, the yellow file of the same relationship is searched with the same blue card, and the first yellow card which matches it is selected.

If the blue card and its matching yellow or pink card bear names neither of whom or both of whom have breast cancer, the matched pair contributes nothing to the solution of the problem. These are designated as "unusable" pairs. But if the blue card and yellow card differ, with the blue card bearing a

name of a relative with breast cancer, while the name on the yellow card does not, such a pair is "usable" and is "favorable" to the hypothesis that women in $P_1$ have more breast cancer than have women from $P_0$. Conversely, if the yellow card bears the name of a relative with breast cancer and the blue card does not, it is again a "usable" pair, but is "unfavorable" to the theory that breast cancer is more prevalent in the experimental population than in the controls.

All matched pairs are entered in books which are kept for the purpose of recording those relatives which have been used and to prevent duplication of use of any one relative. As each usable pair of either favorable or unfavorable type is encountered, it is numbered consecutively and a point is added to the graph. If breast cancer is present in the relative whose name is on the yellow or pink card, (separate graphs are kept for these two groups) the point is plotted along the horizontal line toward the right; if the breast cancer occurred in the relative whose name is on the blue card, the point is plotted diagonally up and to the right. As long as the plotted points lie between the two parallel lines of the graph (figure 1), one continues to obtain more observations; as soon as the plotted points reach or cross the *lower* line, one accepts $H_0$, that the frequency of breast cancer in $P_1$ does not exceed that in $P_0$. If the plotted points reach or cross the *upper* line, $H_1$ is accepted, in this instance, that breast cancer is at least 3 times as great in $P_1$ as in $P_0$.




[FIG. 1. Sequential analysis graph. An example of a sequential analysis graph on which are plotted lines showing the three possible situations. Solid line represents a situation in which the data lead to acceptance of $H_1$. Dotted line represents a situation in which data lead to acceptance of $H_0$. Dot and dash line represents a situation in which the data are insufficient to warrant acceptance of either $H_0$ or $H_1$ and which requires more sampling.

$$\alpha = .05 \qquad \beta = .05$$

The hypothetical ratio of the incidence of breast cancer in $P_1$ to that in $P_0$ has been set at 3:1.

Separate graphs are kept for each relationship, such as mothers, sisters, aunts, grandmothers, first cousins. Actually, the aunts and grandmothers were also plotted each on two graphs, one for paternal and one for maternal relatives. This was done because I desired to ascertain the difference, if any, in the frequency of breast cancer in paternal and maternal relatives.

### VALUES USED IN PLOTTING THE GRAPH

There are four values used in plotting the parallel lines found in figure 1. They are as follows: (1) alpha, $\alpha$,; (2) beta, $\beta$; (3) $u_0$; (4) $u_1$.

The values of $\alpha$ and $\beta$ must be set by the investigator. Before giving the formulas utilizing these four values, a brief explanation may be in order for those who desire to use the method.

### DEFINITIONS OF $\alpha$, $\beta$, $u_1$, AND $u_0$

An idea or an hypothesis may be either true or false. One may do two things with the idea, either accept it or reject it. This gives a four-way classification as to what one may do with an idea; two of these are desirable, two are undesirable. Thus one may

1. Accept an idea which is true<br>4. Reject an idea which is false — Desirable

2. Accept an idea which is false<br>3. Reject an idea which is true — Undesirable

One may put it thus:

The Idea—

| Reaction toward the Idea. | True | False |
|---|---|---|
| *Accept* | Accept Truth 1. | Accept Falsehood 2. |
| *Reject* | Reject Truth 3. | Reject Falsehood 4. |

Number 3 is called an error of the first kind; the risk one is willing to run of making this error is designated as *alpha*. Number 2 is the error of the second kind and the risk which one is willing to run of making this error is designated as *beta*. Both risks may be set at the same significance level, or one may be more than the other. In the problem in human genetics which I am about to describe, I set the levels for alpha and beta at the conventional 5 per cent level. This means that I run a risk of 5 per cent of accepting $H_0$ when $H_1$ is true or of accepting $H_1$ when $H_0$ is true. To those who are inclined to think that they are willing to run no risk of being in the wrong, one can say only that they must spend the rest of their lives collecting all the cases which exist relevant to their problem, and all that may conceivably arise in the future. In other words they will come to no conclusion at all, but perpetually hold

their minds in suspense awaiting the ultimate goal of a complete population analysis of all present and all future populations.

The other two values which enter into the formulas are $u_0$ and $u_1$. These values are the ratios of two ratios to each other. Before setting out the formulas in symbolic terms I will put them into words. The value $u$ in general may be defined as:

$$\frac{\text{the ratio of failures to successes in the experimental population } P_1}{\text{the ratio of failures to successes in the control population } P_0}$$

If a "failure" is regarded as a person with breast cancer, and a "success" as a person without breast cancer, we may rewrite the above as follows:

$$\frac{\text{The ratio of breast cancer cases to those without breast cancer in } P_1}{\text{the ratio of those with breast cancer to those without breast cancer in } P_0}$$

Putting this into symbolic form we may write:

Let $p$ = the probability that women in the general population will develop breast cancer.

Let $p_0$ = the probability that women in $P_0$ (the limited sample of the general population which is serving as a control population) will develop breast cancer.

Let $p_1$ = the probability that women in $P_1$ will develop breast cancer.

$$H_0: p = p_0 = p_1$$

Let $1 - p_0$ = the probability that women in $P_0$ will not develop breast cancer.
Let $1 - p_1$ = the probability that women in $P_1$ will not develop breast cancer.

$$\text{Then } u = \frac{\dfrac{p_1}{1 - p_1}}{\dfrac{p_0}{1 - p_0}} \quad \text{or} \quad \frac{p_1(1 - p_0)}{p_0(1 - p_1)}$$

If $p_0 = p_1$, then $u_0 = 1$; and $H_0: u_0 = 1$ is accepted. Let the difference which is to be looked for in the incidence of breast cancer in the experimental population as compared to that in the control population be designated as $\delta$. I have set the value of delta as 3.0. Then $H_1: p_1 \geqq \delta p_0$ and $\delta > 1$.

$$u_1 = \frac{\dfrac{\delta p_0}{1 - \delta p_0}}{\dfrac{p_0}{1 - p_0}} = \frac{\delta(1 - p_0)}{1 - \delta p_0}$$

Putting these into the terms of my problem,

$$H_1: u_1 = \frac{\dfrac{12}{88}}{\dfrac{4}{96}}$$

or 3.27, a value a little more than delta.

Having explained the four values which enter into the formulas, we can see that in figure 1 we need to know three things: the distances, plus and minus, from zero ($h_1$ and $h_0$) at which the parallel lines cut the ordinate, and $s$, the slope of the lines.

$$h_0 = \frac{\log\left(\frac{1-\alpha}{\beta}\right)}{\log\left(\frac{u_1}{u_0}\right)}$$

$$h_1 = \frac{\log\left(\frac{1-\beta}{\alpha}\right)}{\log\left(\frac{u_1}{u_0}\right)}$$

and

$$s = \frac{\log\left(\frac{1+u_1}{1+u_0}\right)}{\log\left(\frac{u_1}{u_0}\right)}$$

In my problem I have set

$$\alpha = .05$$
$$\beta = .05$$
$$p_0 = .04 \qquad (1 - p_0) = .96$$
$$p_1 = .12 \qquad (1 - p_1) = .88$$
$$\delta = 3.0$$

Therefore

$$h_0 = -2.48$$
$$h_1 = +2.48$$
$$s = .64$$
$$u_1 = 3.27$$
$$u_0 = 1.00$$

The graph, shown in figure, 1 depicts the parallel lines, the formulas for which were given in the preceding pages. The heavy line records a hypothetical sample, which eventually reached 19 usable pairs (of which 4 favored $H_0$ and 15 favored $H_1$) before a decision was reached. The line crosses the acceptance line for $H_1$. Similarly, the dotted line records a hypothetical sample, in which 8 usable pairs were found, (of which 2 favored $H_1$ and 6 favored $H_0$). This line crosses the acceptance line for $H_0$. The third line, dash and dot, records a sample in which 19 usable pairs have been accumulated (11 favoring $H_0$ and 8 favoring $H_1$). No decision has been reached because the line has remained between the two decision lines. This means that further data must be collected before deciding between the two hypotheses.

It should be noted that the frequency of breast cancer in the experimental population might be greater than in the control, but not in as great a ratio

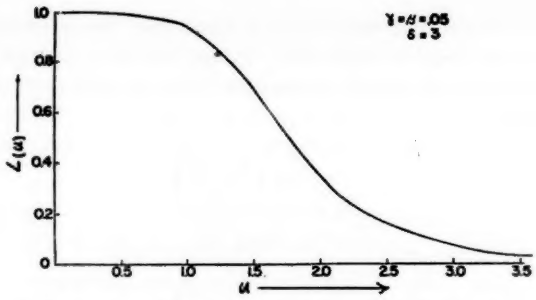



FIG. 2. Graph of OC function. This is the Operating Characteristic Curve for the values chosen in the experiment. For explanation see text.

as the chosen value. The line then might continue to move between the parallel lines necessitating the accumulation of more cases than the investigator is willing to collect. One would reject or accept neither hypothesis, but would examine the data to find what value of $u$ they indicated.

A curve, known as the Operating Characteristic Curve is described by Wald which shows the probability of accepting a value of $u = 1$ (equality of frequency of breast cancer in the two populations) as a function of the true value. In the case of the chosen value 3, and corresponding to a $u$ value of 3.27, the OC curve shows that the probability of accepting a value of $u = 1$ when it is in fact 1, is of course 0.95 (since I have set the risk of rejecting $u = 1$ when it is 1 at alpha $= 0.05$). The probability of accepting $u = 1$ when it is in fact 1.5 is about 0.7; of accepting that it is 1 when it is in fact 2 is about 0.35; and of accepting that it is 1 when it is in fact 3.27 is 0.05 (corresponding to the value of beta which I have set at 0.05). Thus the chance of accepting $H_0$ decreases gradually as the true value of $u$ increases. Conversely, the chance of accepting $H_1$ gradually increases. For a discussion of the Operating Characteristic Curve and its derivation one should refer to Wald's original text.

Two facts should be pointed out here. The first is that the method of sequential analysis involves alternative hypotheses; that rejection of one automatically entails acceptance of the other. Thus, in terms of the problem on breast cancer, if I reject the hypothesis of as little breast cancer in $P_1$ as in $P_0$, I accept the hypothesis that there is at least 3 times as much in $P_1$. Conversely, if I reject the hypothesis that there is 3 times as much, I accept the idea that there is as little in $P_1$ as in $P_0$.

Second, the primary purpose of the method is not to estimate how great the difference between the two populations is, (although that extension of the method is said now to be available), but to minimize the size of sample necessary to arrive at a statistically valid conclusion. The difference between the two populations can be estimated from the actual data; but the sequential analysis

method enables one to say that the difference is or is not as great as the value of *u* chosen within the limit of the designated risks of accepting a false or rejecting a true hypothesis set by the investigator. It can be shown, with the particular values used in figure 1, that if the first 4 breast cancers were found in $P_0$, $H_0$ will be accepted; similarly, if the first 7 breast cancers were found in $P_1$, $H_1$ would be accepted. What are the probabilities that one will obtain the first four breast cancer cases favorable to $H_0$ if $H_1$ were true, and similarly, the first 7 breast cancer cases favorable to $H_1$ if $H_0$ were true?

If the frequency of breast cancer is the same in $P_0$ and $P_1$, ($H_0$ is true), the probability of the first 4 cases being in favor of $P_0$ is $1/16$, $(1/2)^4$. But if breast cancer is 3 times as frequent in $P_1$ as in $P_0$, ($H_1$ is true), the probability of obtaining the first 4 cases from $P_0$ is only $1/256$. Similarly, if the frequency of breast cancer is the same in $P_0$ and $P_1$, ($H_0$ is true), the probability of obtaining the first 7 cases from $P_1$ is only $1/128$ $[(1/2)^7]$. On the other hand, if the frequency of breast cancer is 3 times as great in $P_1$ as in $P_0$, ($H_1$ is true), the probability of having the first 7 cases come from $P_1$ is about $2/15$ or $(3/4)^7$, or 17 times as great. Thus, although the minimal number of cases needed for acceptance of $H_1$ is small, the probability of obtaining such a run of favorable cases is also small in the event of equality in the amount of breast cancer in $P_1$ and $P_0$, but rises rapidly as the frequency of breast cancer in $P_1$ rises above that in $P_0$.

Changes in the values of alpha, beta, and delta alter the number of usable cases needed to come to a decision. Keeping the first two values constant, and increasing delta *decreases* the distance between the lines, and makes the slope of the lines steeper. Similarly, increasing the values of either alpha or beta or both, *decreases* the distance between the lines. The value of delta which is chosen should be one which is small enough to detect any difference considered large enough to be worth detecting if it exists.

## SUMMARY

The method of sequential analysis minimizes the number of cases needed for a statistically valid conclusion. Hence the method is economical in time and money. It is adapted to human genetic problems in which data from two populations are being compared.

Confidence intervals for $p$ can be worked out for such problems.

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# Inheritance of Nephrogenic Diabetes Insipidus

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NEPHROGENIC DIABETES INSIPIDUS is a congenital disease of the kidneys, in which the renal tubules fail to respond to antidiuretic hormone. There is a continual excretion of a large volume of dilute urine. This results in excessive thirst, and if sufficient water is not consumed the patient rapidly becomes dehydrated and feverish.

The disease becomes apparent in early infancy, when it is characterized by failure to thrive and develop normally, attacks of unexplained fever, vomiting, and constipation. The polyuria may not be as noticeable in an infant as in an older child, though the mother may remember that the baby's diapers always seemed to be wet. Thirst, too, is not an easily recognizable symptom in a young infant, though water if offered between feedings will be taken avidly.

When an infant is seen with these symptoms, it can readily be demonstrated that polyuria exists by collecting a 24-hour urine sample and noting the large volume (2–3 liters even in a small infant) and low specific gravity. If, then, fluids are withheld for 6–12 hours, the baby will show signs of dehydration, become feverish, and although the urine volume may diminish, the specific gravity will not rise significantly. Further tests can be carried out to rule out chronic nephritis and adrenocortical failure as causes of the polyuria. A diagnosis of "diabetes insipidus" can then be made. This condition is usually due to a failure of the hypothalamic-posterior pituitary system to produce anti-diuretic hormone, occurring as a congenital defect or as a result of some disease process involving that region. When an individual with "pituitary" diabetes insipidus is given anti-diuretic hormone in the form of injections of posterior pituitary extract, the polyuria is at once overcome. In contrast a patient with "nephrogenic" diabetes insipidus does not respond to such injections, and continues to excrete a large volume of dilute urine. The latter type of patient, then, is thought to have a specific defect of the renal tubules, which renders them unable to respond to the stimulus of anti-diuretic hormone by reabsorbing more water.

The disease is quite compatible with long life provided sufficient water can always be obtained. If water is long withheld, there is a rapid progression through dehydration to shock and death. There is no specific corrective treatment, and the patient must simply be provided with sufficient water to make up for the excessive urinary loss.

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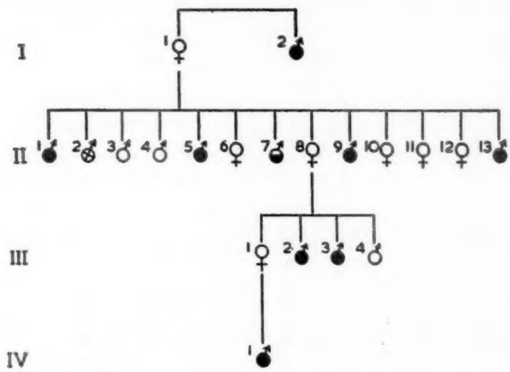
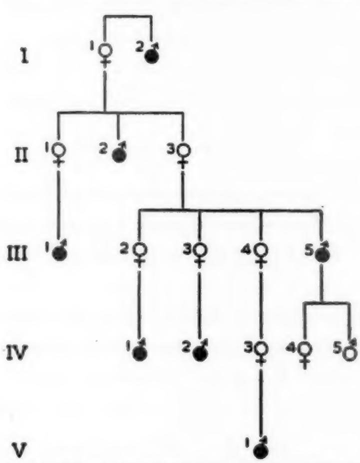
NEPHROGENIC DIABETES INSIPIDUS



Pedigree J (in part) of Forssman (1945) showing affected members only

FIG. 1

NEPHROGENIC DIABETES INSIPIDUS



Pedigree (in part) of Williams and Henry (1947) showing affected members only

FIG. 2

## PATTERN OF INHERITANCE

The pattern of inheritance of *nephrogenic diabetes insipidus* is based on meagre data. Forssman (1945) traces the anomaly through four generations with nine affected men and three carrier women (Fig. 1); Williams and Henry (1947) through five generations with seven affected men and seven carrier

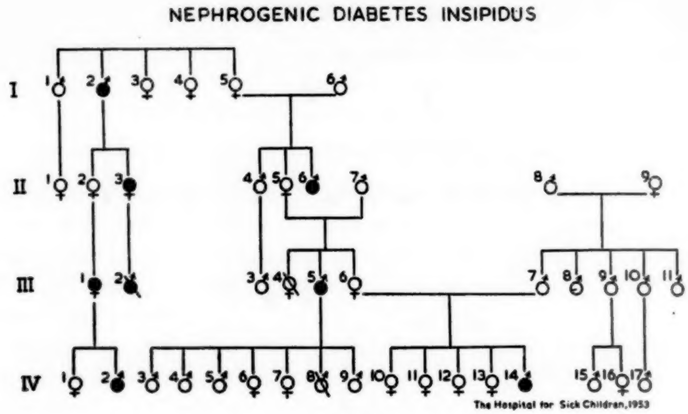



Fig. 3

women (Fig. 2). Waring et al. (1945) cite a pedigree of three affected half-brothers born to two fathers and a carrier mother. By one of the fathers there was also a normal sister. A single case of an affected girl born out-of-wedlock, is reported by Dancis et al. (1948). The possibility of this child being the offspring of a consanguineous union must be kept in mind. These data suggest that the pattern of inheritance is that of a single recessive sex-linked gene.

## PRESENT PEDIGREE

The families of the present pedigree are farmers of Scottish and Irish descent, early settlers in Nova Scotia, Canada, living in rather isolated communities with little medical care. Only part of the pedigree (Fig. 3) has therefore been documented.

The immediate family moved to Barrie, Ontario, and the proband (IV-14), a boy of three months, was admitted to the Hospital for Sick Children for investigation of unexplained fever and failure to thrive. The pregnancy and delivery had been normal, and the birth weight was eight pounds twelve and three-quarter ounces.

During his first two weeks of life he had been breast-fed and had seemed to develop well. He was then weaned to an evaporated milk formula because his mother suffered a severe attack of "flu", and from that time he had never seemed to progress well. His appetite was poor, his weight gain slow, and there were periods of vomiting and frequent bouts of fever. At two and a half months of age he was admitted to another hospital, where his temperature was found to vary from 99° to 101° daily, with occasional spikes to 104°. No evidence of infection could be found, and he was treated with penicillin followed by aureomycin without benefit.

On admission to the Hospital for Sick Children his weight was ten pounds eight ounces, temperature 100°. He appeared pale and slightly undernourished and his skin was dry. There was a little yellowish nasal discharge, but no other evidence of infection, and examination of the heart, lungs, abdomen and external genitalia was normal. The blood counts showed a moderate anemia and the blood smear was normal. Tuberculin and Wassermann tests were negative, as were agglutination tests for typhoid, paratyphoid, and undulant fever. He was treated with intravenous fluids, and improved, but when they were stopped he soon became dehydrated and had a low-grade fever. As there was no loss of fluid by vomiting or diarrhea, excessive urinary loss of water was suggested, and it was at this point that the interesting family history was obtained. Further investigation then showed a constant polyuria, inability to concentrate the urine even when fluids were withheld for 12 hours (during which time he lost fifteen ounces in weight, his temperature rose to 101°, and he showed clinical signs of dehydration). An injection of pitressin caused no decrease in urine flow or increase in specific gravity. A cystogram and intravenous pyelogram were normal. X-rays of the skull were normal. A diagnosis of nephrogenic diabetes insipidus was made.

He was treated by offering fluids *ad lib.* between feedings, and at once his temperature returned to normal and he became more active and began to gain in weight. He was discharged to the care of his family doctor, and has continued to develop normally at home. He is now a fine, healthy boy nearly two years old, well cared for by his family. Each night he drinks two quarts of water, with the result that his mother's rest is continually broken in caring for him and her health has thereby suffered.

The family trace their anomaly through four generations (Fig. 3). There is no question that the maternal uncle is affected (III-5). Documented evidence is on file with the Canadian Army. He drinks eight quarts of water during the night. Nor is there any doubt that the brother of the maternal grandmother was affected (II-6), as well as the brother of the maternal great-grandmother (I-2). It is clear, therefore, that the mother, grandmother and great-grandmother are all carriers.

Further investigations and documentation should be made concerning the descendants of I-2, to be certain that he did have an affected daughter (II-3) who gave birth to an affected son (III-2). Also did his granddaughter (III-1) become affected at the age of twelve years and has she an affected son (IV-2)?

## SUMMARY

The clinical features of nephrogenic diabetes insipidus are described. Meagre published data are reviewed and a family is here presented with affected members in four generations. The data suggest that the pattern of inheritance is that of a single recessive sex-linked gene.

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# BOOK REVIEWS

## *Clinical Genetics*

### Edited by Arnold Sorsby, London, England: Butterworth & Co., Ltd., St. Louis, Mo.: The C. V. Mosby Company, 1953, Pp. 580 + 23, $17.50.

THIS RECENT BOOK easily qualifies as the best text in its field. Dr. Sorsby, its editor, has utilized the collaboration method of authorship, with more than thirty able contributors from a half a dozen different countries. This type of authorship, so popular now in the clinical fields of medicine, is especially rewarding in clinical genetics, where few, if any, individuals can be said to be qualified authorities on all pertinent subjects.

This book is divided into two sections, "Theoretical Consideration" and "Clinical", the latter exhibiting a 3:1 dominance as far as pages are concerned. The first section is the better written and organized, probably because these are the topics which have been mulled over by numerous authors in recent years. Such topics as twin studies, mutation, and cytogenetics are all clearly and interestingly discussed. Data from experimental animal and plant genetics have been included to great advantage. The second section surveys the whole realm of human hereditary traits, pathological as well as normal. This is done largely by body systems, with special chapters for such general topics as metabolic disorders, infectious diseases, and cancer.

In his introduction, Sorsby states "Only in extreme cases can hereditary and environmental factors be clearly disentangled in the effect they produce, and there is in fact much over-lap." However, some of the contributors appear to differ somewhat in their thoughts on this matter. Thus, allergy is interpreted by several writers in rather simple terms (p. 50, 554), with little being said regarding the extreme range of expressivity. Choanal atresia is described as a probable dominant trait on minimal evidence (p. 426). On the other hand, the statement is made that for fibrocystic disease of the pancreas there is no definite conclusion regarding the mode of inheritance (p. 415), and the mode of inheritance of the infantile form of familial amaurotic idiocy (Tay-Sachs) is described as uncertain (p. 197). Readers with experience in the field of medical genetics will find a number of statements and interpretations with which to disagree. This reflects more on the present clumsy body of knowledge called clinical genetics than on the accuracy of the writers, however.

In a number of instances the subjects have been dealt with rather inadequately. Cystinuria is apparently viewed as a single entity (p. 183), a misleading assumption. Likewise, glycogen storage disease is also viewed as an entity (p. 189), contrary to clinical observations. A number of subjects are accorded space far out of proportion to their relative importance. Thus, four pages are devoted to congenital pyloric stenosis as compared to one-half a page for rheumatoid arthritis. The index, which should be exceptionably complete in a reference text, is rather weak in the present case. For example, there is no listing of "rheumatic fever" or "Tay-Sachs Disease." "Propositus" and "proband", terms familiar to the geneticist but not to the physician, are neither listed in the index nor defined in the text. The book could well have included a short glossary, particularly for the use of the nongeneticist reader.

It is somewhat difficult to identify any particular group for whom this book was prepared. It will not be a very practical book for either the general medical practitioner or the medical specialist, being too technical in some portions and too superficial in others. The section on theoretical considerations is excellent, but presupposes that the reader

already has a knowledge of genetic principles. The section on clinical aspects is often incomplete. It is as if this book is directed towards the geneticist interested in medicine rather than the physician interested in genetics.

In spite of various shortcomings, this book is indeed a most valuable reference book for anyone interested in human genetics, and will be widely used and quoted. Its price may discourage many potential buyers who are not in a position to appreciate its stature as a science classic. Its authors include a majority of the leading workers in the field of human genetics, thereby adding to its prestige and authoritativeness. The book is of convenient size, well printed, and reads easily. Congratulations are offered the editor of this truly international text, with hopes that he will capitalize on this excellent start by planning ahead now for the later editions that future years will undoubtedly require.

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## *Heredity in Health and Mental Disorder*

By Franz J. Kallmann. New York: W. H. Norton, 1953, pp. 315, $6.00.

In the autumn of 1952 Dr. Kallmann delivered the annual Thomas William Salmon Memorial Lectures at the New York Academy of Medicine. This book is the published version of these lectures. The Salmon Lectures have consistently produced outstanding summaries of various fields of interest and accomplishment in psychiatry, and Dr. Kallmann's contribution adds measurably to the already excellent reputation enjoyed by this series.

As this book is intended for a wide audience, a brief but highly competent discussion of the history and general principles of genetics is given. There is also an account of the methods of genetic investigation applicable to man, with a detailed discussion of the advantages of the twin-family method which has been developed and used so effectively by Dr. Kallmann. Very interesting data are given concerning comparisons of normal traits of personality, intellect and physique in twin pairs studied by this technique.

The author is well known for his extensive investigations of genetic factors concerned in the major psychoses, especially schizophrenia, which have engaged his attention for more than twenty years. The major portion of this work is devoted to presentation of the results of the author's studies in schizophrenia, manic-depressive psychosis, involutional psychosis, convulsive states and other conditions. The findings of other investigators in this field are also summarized, evaluated and compared. Extensive data are given, based on large numbers of families studied, concerning expectancy rates for development of specified types of psychosis in relatives of various degrees. These data are extremely valuable to those concerned with genetic counseling or marriage counseling of any type, as they provide useful empiric risk figures. The genetic analysis is excellent and the conclusions reached are well supported by the data.

In the final section Kallmann turns his attention to the role that may be played by genetics in public health planning. Certain problems concerned with population genetics and eugenics are discussed. From the point of view of preventive medicine, this reviewer is particularly impressed by the potential usefulness of Kallmann's risk figures in preventing or minimizing the effects of a morbid genotype. As it is possible to recognize at birth many of those with a high probability of having a specific predisposition to the development of psychosis, important new fields in mental hygiene and disease prevention are opened.

Better evaluation of environmental and biochemical factors effective in inducing mental breakdown in genetically susceptible persons should provide better methods of prevention and more rational methods of treatment. Kallmann's studies of monozygous twin pairs discordant for psychosis provide an important first step in this direction.

It is to be hoped that this book will become required reading for psychiatrists. It provides a reorientation and better perspective for much work in this field. There has been a regrettable tendency in some quarters for investigative work to completely ignore the existence of genetic and constitutional factors in the etiology of the psychoses. The incorporation of the genetic approach into many areas of study should contribute greatly to future progress.

The publishers have contributed to the success of this volume by providing an attractive format and a coated paper for clear reproduction of the 89 photographs and 20 tables which illustrate the text. A carefully prepared index and an extensive bibliography add to its usefulness as a reference work.

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## *Advances in Genetics. Vol. V.*

By M. Demerec (Ed.), New York, Academic Press, 1953, pp. 331, $8.50.

The continued healthy growth of the science of genetics has witnessed an accompanying increase in the number of organisms studied, as well as in the number and refinement of techniques employed. This increasing ramification of materials and methods brought to bear on fundamental questions in genetics necessitates periodic succinct and authoritative reviews of important topics. Such a need is admirably met by the annual series, "Advances in Genetics," of which the fifth, most recent, volume is under review.

Of the six articles in this volume, two deal with the formal and biochemical genetics of the silkworm, written, respectively by Y. Tanaka and H. Kikkawa. Since much of the information on the silkworm has been accumulated by Japanese investigators, Tanaka and Kikkawa have performed a noteworthy service in organizing and making available a good deal of knowledge heretofore restricted to Japanese language publications. As is made clear by Tanaka and Kikkawa, the silkworm is of genetic as well as of economic interest. According to Tanaka, 15 linkage groups out of a total of 28 chromosomes have been identified. A large number of mutants are described, some loci with large numbers of alleles, such as the E group of Chromosome VI concerned with the occurrence and distribution of larval markings. Such allelic series might prove useful in expanding our knowledge of pseudoallelism. As for the biochemical genetics of the silkworm, Kikkawa's paper extends our knowledge of gene-enzyme relations in connection with problems relating to the formation in various stages of development of brown pigment from tryptophan, the synthesis of tryptophan and nicotinic acid, genic control of the production of various integumentary pigments and of amylase in the larval digestive and body fluids. Especially striking is Kikkawa's account of genes which control the selective permeability of silk-gland cells to carotenoids.

Two articles summarize advances in the genetics of microorganisms. A. D. Hershey considers in concise fashion the hereditary transmission of characters in bacteriophage with emphasis on such problems as genetic recombination and heterozygosis. A review in monographic style, dealing with the genetics of the fungus Aspergillus nidulans, is presented by G. Pontecorvo and his associates. The life cycle, culturing methods, isolation of mutants,

methods of genetic analysis and formal genetics are given detailed consideration. Of especial interest is the discovery that a self-fertile or homothallic strain can engage in preferential outcrossing, i.e., relative heterothallism. In addition, the authors have provided information on pseudoallelism in connection with the bi and paba loci. Other phenomena of great interest are discussed. For example, the authors have succeeded in producing strains whose vegetative cells contain diploid nuclei heterozygous for known loci. This in turn has led to their observation of mitotic segregation, which might well enhance our understanding of somatic segregation in plants and in higher animals. Moreover, it now becomes possible to compare the physiological activities of gene sets in two different spatial distributions, that is, in the diploid condition and in the heterokaryotic condition involving a mixed population of haploid nuclei.

In connection with problems of genetics and evolution, two articles are devoted to considerations of natural populations. E. B. Ford reviews the Genetics of Polymorphism in the Lepidoptera, and emphasizes the distinction between *balanced polymorphism* due to a balance of selective agencies favoring diversity and *transient polymorphism* existing only during a period of gene spread and displacement of its allele. The latter type is strikingly exemplified by industrial melanism. Finally, an account of Population Dynamics of Rodents and Other Small Mammals is furnished by W. Frank Blair. Although no genetic information as such is presented, the behavior of members of a natural population is an important factor to be considered in connection with the problem of gene flow. Topics such as home-range behavior; the effects of sex, age, food habits, season and population density on home-range size; patterns of reproductive behavior and of distribution should prove to be of special interest to students of the population genetics of small mammals.

It seems clear that the current volume has much to recommend it, and it should prove useful in helping geneticists to maintain a broad outlook commensurate with the broad scope of genetics itself.

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## *Rh-Hr Blood Types. Applications in Clinical and Legal Medicine and Anthropology*

By A. S. Wiener, New York: Grune and Stratton, 1954, Pp. 763 + xii, $11.50

IT SHOULD BE STATED at the outset that this is not a new book on the Rh-Hr blood types. It is a reprint of 72 papers by Dr. A. S. Wiener, alone or with various collaborators, two papers signed by Dr. I. B. Wexler, and 10 sets of directions, of the sort Dr. Wiener sends out with serum from his laboratory, for the technique of tests for Rh and other new blood types. The total material presented amounts to some 350,000 words. In 18 cases papers are accompanied by brief editorial comment by Dr. Wiener (about 1200 words). In addition there is a preface, a bibliography of the author's papers down to October 1953, an author index, and a subject index (both good).

Although the reviewer can not but regret that the author did not tackle the herculean task of writing a systematic exposition of the development and present state of the Rh blood groups and the other new blood groups discovered since then (a task for which Dr. Wiener is surely as well fitted as anybody in the world), he hastens to admit that, since this book has not been written, the present volume is the next best thing. In it the reader will find traced the development of the Rh problem, from its first mention by Landsteiner

and Wiener in January 1940, down to 1953, at least in so far as the development was due to Dr. Wiener's work. And perusal of the book impresses even one who has followed the subject closely, as the reviewer, with the tremendous value, both in originality and in quantity of material, of Dr. Wiener's contribution. Merely the variety of subjects covered is amazing. In addition to the discovery of the Rh factors and their role in transfusion and (following Levine's work) in pregnancy, one finds good discussions of the genetics of these and other factors, methods of calculation of gene frequencies, discussions of the effect of natural selection on the blood groups, derivations of the variance of estimated frequencies, discussions of the anthropological aspects (to which Dr. Wiener has made notable contributions), discussions of the medico-legal applications (a field in which the author is pre-eminent), and of course extensive descriptions and discussions of technique.

The papers reprinted are not limited to Rh. Other new blood groups are discussed, especially in the section on technique, and there is some material on the ABO and MNS blood groups, and discussions of the structure of the blood agglutinogens and the origin of the isohemagglutinins.

The bibliography of Dr. Wiener's papers is an impressive item in itself. His first paper appeared in 1929, and the paper announcing the discovery of Rh was number 63. The October 1953 paper is number 333, meaning a publication of over 270 papers in 14 years, an average of nearly 20 papers per year. In the year 1946 there were 36 papers. This is indeed a colossal record of investigation and industry, and would constitute an imperishable monument to the author even if he never wrote another paper.

It is inevitable that a book constructed in the manner of this one will suffer from drawbacks of obsolete passages, superseded notations, and repetitions, but the total effect of these factors is surprisingly slight, and the reader is left with a strong impression of the continuing vitality of Dr. Wiener's contributions. However, two sorts of repetition are apparent. The first concerns the use of diagrams, always a prominent feature of Dr. Wiener's exposition, particularly diagrams designed to show that "incomplete" or "blocking" antibody is univalent, being in fact just half an ordinary agglutinating antibody. The diagrams are neat and suggestive, but to this reviewer do not carry the conviction of a laboratory demonstration. The second repetitious feature of course concerns Dr. Wiener's trenchant opposition to the Fisher-Race CDE notation. Dr. Wiener did not approve of this in the beginning, and his feelings toward it have obviously not become any more cordial with time. However, a book with no attempt to demolish CDE would not seem like Dr. Wiener, and it is an advantage to have his various arguments marshalled in one book.

It may be confidently predicted that few, if any, of those attempting work in the field of blood groups will feel they can do without Dr. Wiener's new book.

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## *An Rh-Hr Syllabus. The Types and their Applications.*

By A. S. Wiener, New York: Grune and Stratton, 1954, Pp. 82 + xii, $3.75.

This book is essentially a series of definitions of terms of common occurrence in Dr. Wiener's writing about the Rh-Hr blood groups. A paragraph or two is devoted to each term. The subjects are grouped into 8 chapters; Fundamentals, Rh antibodies, Serology and Genetics of the Rh-Hr types, Erythroblastosis fetalis, Blood transfusion, Autosensitization, Anthropologic aspects, and Medicolegal applications. The author states this volume is intended to

serve as a convenient introduction to the larger volume reviewed above. Readers not already familiar with Rh might well find the smaller book of great help in understanding the terminology employed in the larger one. Under appropriate headings the rules of Rh-Hr inheritance and tables of racial incidence are given. There are several diagrams, one of them appearing twice. The reader will not find this book of much help in understanding the publications of the British workers; the Fisher-Race notation is mentioned only to disparage it. The book has a brief index.

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# BIBLIOGRAPHY OF HUMAN GENETICS

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THIS section is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made and is being made to make the list complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or any current reference which it seems probable may be missed as a result of its appearance in a journal which is probably not systematically covered by the bibliographic editor. If a reference to an article is sent in, be sure that it is complete with respect to name of author(s), year of publication, title of article, name of journal, volume number, issue number, and first and last page numbers. If the reference is to a book, be sure that it includes name of author(s), date of publication, title, name of publisher, place of publication, and number of pages.

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